Supporting Information

Copper-Catalyzed One-Pot Synthesis of α-Functionalized Imidates

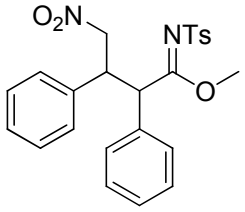
Ralph Husmann,[b] Yun S. Na,[a] Carsten Bolm*[b] and Sukbok Chang*[a]

[a] *Department of Chemistry and Molecular-Level Interface Research Center, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, Republic of Korea. Fax: +82 42 350 2810; Tel:+82 42 350 2841; E-mail: sbchang@kaist.ac.kr*

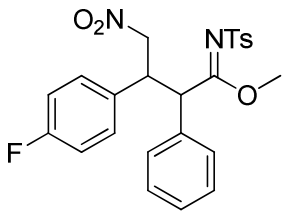
[b] *Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany. Fax:+49 241 8092391; Tel: +49 241 8094675; E-mail: carsten.bolm@oc.rwth-aachen.de*

General information: Unless otherwise stated, all commercial reagents and solvents were used without additional purification, and all reactions were performed under nitrogen atmosphere in dried glassware. All solvents and Et_3N were dried and distilled according to standard procedures. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254} plates. Visualization on TLC was achieved by the use of UV light (254 nm) and treatment with phosphomolybdic acid or ceric ammonium molybdate stain followed by heating. Column chromatography was undertaken on silica gel (Merck Kieselgel 60 F_{254} 400-630 mesh). ^{1}H NMR was recorded on Bruker FT AM 400 (400 MHz) or Varian Inova 400 (400 MHz). Chemical shifts are quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants, *J*, were reported in hertz unit (Hz). ^{13}C NMR was recorded on Bruker FT AM 400 (100 MHz) or Varian Inova 400 (100 MHz) and was fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.0 ppm of chloroform-*d*. Infrared (IR) spectra were recorded neat in 0.5 mm path length using a sodium chloride cell on Bruker EQUINOX 55. Frequencies are given in reciprocal centimeters (cm^{-1}) and only selected absorbance is reported. Melting points were measured with a Barnstead Electrothermal apparatus (12V, ~50/60Hz, 45W Fuse, made in UK). High resolution mass spectra were obtained from the Korea Basic Science Institute (Daegu) by using EI or FAB methods.

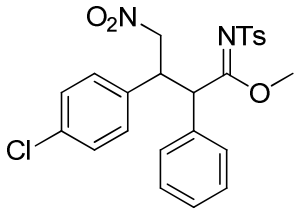
Representative procedure for the synthesis of α-functionalized imidates (Table 1, 2 and 3). To a mixture of CuI (9.5 mg, 0.05 mmol), *p*-toluenesulfonyl azide[1] (118.3 mg, 0.60 mmol) and *trans*-β-nitrostyrene (75 mg, 0.50 mmol) in THF (1.5 mL) was slowly added phenylacetylene (66 μL, 0.60 mmol) methanol (101 μL, 2.5 mmol) and triethylamine (208 μL, 1.5 mmol) at room temperature under an N_2 atmosphere. After 24 h, the reaction mixture was diluted with CH_2Cl_2 (3 mL) and quenched with a sat. NH_4Cl-solution (3 mL) and a 1N HCl-solution (3 mL). The mixture was stirred for an additional 30 minutes and then the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography using silica gel with *n*-hexane/ethyl acetate = 5/1 as eluent to afford the desired product.



Methyl 4-nitro-2,3-diphenyl-*N*-tosylbutanimidate (Table 2, entry 1): yellowish solid (73%), m.p. 161-162 °C, R_f = 0.37 (*n*-hexane/ethyl acetate = 3/1); d.r. = 58 : 42; NMR: δ_H (400 MHz, $CDCl_3$) 7.84 (d, 1H, *J* = 8.3 Hz), 7.70 (d, 1H, *J* = 8.3 Hz), 7.55 (d, 1H, *J* = 8.3 Hz), 7.42-7.29 (m, 6H), 7.18-7.12 (m, 5H), 5.52 (d, 0.5H, *J* = 11.9 Hz), 5.28 (d, 0.5H, *J* = 11.6 Hz), 4.97-4.91 (dd, 0.5H, *J* = 10.2 Hz, 12.8 Hz), 4.72-4.68 (dd, 0.5H, *J* = 4.6 Hz, 12.8 Hz), 4.53-4.48 (m, 0.5H), 4.35-4.28 (m, 1.5H), 3.77 (s, 1.5H), 3.48 (s, 1.5H), 2.41 (s, 1.5H), 2.35 (s, 1.5H); δ_C (100 MHz, $CDCl_3$) 172.9, 170.9, 143.6, 138.4, 136.6, 136.3, 134.2, 129.4, 129.4, 129.3, 129.1, 129.0, 128.8, 128.8, 128.6, 128.4, 128.1, 128.0, 127.9, 127.8, 126.6, 126.4, 79.0, 78.7, 56.0, 55.4, 53.0, 51.0, 47.2, 47.1, 21.4, 21.3; IR (film): ν_{max}/cm^{-1} 601, 686, 702, 738, 815, 947, 1017, 1092, 1154, 1254, 1290, 1302, 1379, 1438, 1456, 1496, 1506, 1556, 1597, 1612, 1653; HRMS (EI) m/z calcd. for $C_{24}H_{24}N_2O_5S$ $[M+H]^+$: 452.1406, found: 452.1409.

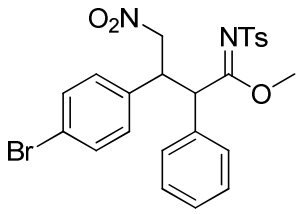


Methyl 3-(4-fluorophenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (Table 2, entry 2): yellowish solid (69%), R_f = 0.34 (*n*-hexane/ethyl acetate = 3/1); d.r. = 54 : 46; NMR: δ_H (400 MHz, $CDCl_3$) 7.82 (d, 1H, *J* = 8.3 Hz), 7.67 (d, 1H, *J* = 7.4 Hz), 7.57 (d, 1H, *J* = 8.3 Hz), 7.43-7.28 (m, 4.5H), 7.19-7.10 (m, 3.5H), 7.02-6.97 (m, 1H), 6.85-6.81 (m, 1H), 5.45 (d, 0.5H, *J* = 12.0 Hz), 5.22 (d, 0.5H, *J* = 11.6 Hz), 4.94-4.88 (dd, 0.5H, *J* = 10.5 Hz, 12.8 Hz), 4.70-4.65 (m, 0.5H), 4.52-4.46 (m, 0.5H), 4.34-4.25 (m, 1.5H), 3.78 (s, 3H), 3.50 (s, 3H), 2.40 (s, 3H), 2.35 (s, 3H); δ_C (100 MHz, $CDCl_3$) 172.7, 170.8, 162.3 (d, ^1J = 245.7 Hz), 162.0 (d, ^1J = 245.5 Hz), 143.7, 143.4, 138.4, 138.3, 134.1, 134.0, 132.3 (d, ^4J = 3.1 Hz), 132.1 (d, ^4J = 3.1 Hz), 129.9 (d, ^3J = 8.1 Hz), 129.6 (d, ^3J = 8.2 Hz), 129.4, 129.3, 129.2, 129.0, 128.5, 128.0, 126.6, 126.4, 115.8 (d, ^2J = 21.4 Hz), 115.7 (d, ^2J = 21.4 Hz), 78.8, 78.6, 56.1, 55.5, 53.0, 51.1, 46.6, 46.4, 21.4, 21.4; IR (film): ν_{max}/cm^{-1} 604, 685, 736, 813, 839, 948, 1016, 1092, 1153, 1226, 1289, 1379, 1439, 1512, 1554, 1611; HRMS (EI) m/z calcd. for $C_{24}H_{23}FN_2O_5S$ $[M+H]^+$: 470.1312, found: 470.1313.

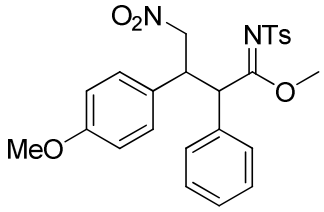


Methyl 3-(4-chlorophenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (Table 2, entry 3): yellowish solid (60%), R_f = 0.43 (*n*-hexane/ethyl acetate = 3/1); d.r. = 56 : 44; NMR: δ_H (400 MHz, $CDCl_3$) 7.82 (d, 1H, *J* = 8.2 Hz), 7.66 (d, 1H, *J* = 6.9 Hz), 7.56 (d, 1H, *J* = 8.2 Hz), 7.45-7.24 (m, 5.5H), 7.22-7.06 (m, 4.5H), 5.44 (d, 0.5H, *J* = 11.8 Hz), 5.22 (d, 0.5H, *J* = 11.8 Hz), 4.95-4.87 (dd, 0.5H, *J* = 10.4 Hz, 12.9 Hz), 4.70-4.64 (dd, 0.5H, *J* = 4.5 Hz, 12.9 Hz), 4.52-4.45 (m, 0.5H), 4.35-4.24 (m, 1.5H), 3.79 (s, 1.5H), 3.53 (s, 1.5H), 2.42 (s, 1.5H), 2.37 (s, 1.5H); δ_C (100 MHz, $CDCl_3$) 172.4, 170.5, 143.7, 143.3,

138.2, 138.2, 135.0, 134.8, 134.0, 133.9, 133.8, 133.6, 129.5, 129.4, 129.4, 129.3, 129.2, 129.2, 129.0, 128.9, 128.9, 128.8, 128.5, 128.0, 126.6, 126.3, 78.7, 78.4, 56.2, 55.6, 52.9, 51.0, 46.7, 46.6, 21.6, 21.5; IR (film): ν_{max}/cm^{-1} 681, 743, 813, 915, 946, 1015, 1091, 1152, 1187, 1253, 1292, 1378, 1438, 1493, 1553, 1597; HRMS (ESI) m/z calcd. for $C_{24}H_{23}ClN_2O_5S$ $[M+H]^+$: 487.1089, found: 487.1093.



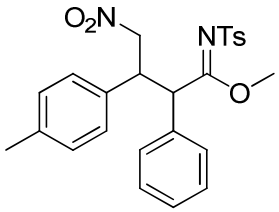
Methyl 3-(4-bromophenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (Table 2, entry 4): yellowish solid (65%), R_f = 0.37 (*n*-hexane/ethyl acetate = 3/1); d.r. = 54 : 46; NMR: δ_H (400 MHz, $CDCl_3$) 7.81 (d, 1H, *J* = 8.3 Hz), 7.65(d, 1H, *J* = 6.9 Hz), 7.55 (d, 1H, *J* = 8.4 Hz), 7.44-7.27 (m, 6.5H), 7.21-7.12 (m, 2.5H), 7.03-6.99 (m, 1H), 5.43 (d, 0.5H, *J* = 11.7 Hz), 5.21 (d, 0.5H, *J* = 11.6 Hz), 4.92-4.86 (dd, 0.5H, *J* = 10.4 Hz, 12.9 Hz), 4.67-4.63 (dd, 0.5H, *J* = 4.5 Hz, 12.9 Hz), 4.50-4.43 (m, 0.5H), 4.31-4.24 (m, 1.5H), 3.78 (s, 1.5H), 3.52 (s, 1.5H), 2.41 (s, 1.5H), 2.38 (s, 1.5H); δ_C (100 MHz, $CDCl_3$) 172.5, 170.6, 143.8, 143.5, 138.4, 138.3, 135.7, 135.5, 134.0, 133.9, 132.0, 131.9, 129.9, 129.7, 129.5, 129.5, 129.3, 129.0, 129.0, 128.6, 128.2, 126.7, 126.4, 122.4, 121.9, 78.7, 78.4, 56.2, 55.6, 52.8, 50.9, 46.7, 46.6, 21.5, 21.5; IR (film): ν_{max}/cm^{-1} 603, 686, 707, 739, 814, 948, 1012, 1092, 1155, 1184, 1254, 1289, 1378, 1440, 1492, 1554, 1621, 2951; HRMS (EI) m/z calcd. for $C_{24}H_{23}BrN_2O_5S$ $[M+H]^+$: 532.0493, found: 532.0499.



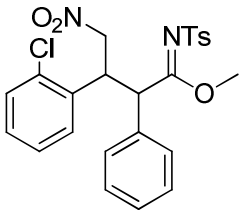
Methyl 3-(4-methoxyphenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (Table 2, entry 5): yellow solid (62%), m.p. 99-100 °C, R_f = 0.37 and 0.27 (*syn* and *anti* diastereoisomer, respectively, *n*-hexane/ethyl acetate = 3/1).

Syn isomer: NMR: δ_H (400 MHz, $CDCl_3$) 7.75 (d, 2H, *J* = 8.4 Hz), 7.28-7.21 (m, 4H), 7.11-7.03 (m, 3H), 6.98 (d, 2H, *J* = 8.7 Hz), 6.60 (d, 2H, *J* = 8.8 Hz), 5.15 (d, 1H, *J* = 11.6 Hz), 4.84-4.78 (dd, 1H, *J* = 10.2 Hz, 12.4 Hz), 4.59-4.55 (dd, 1H, *J* = 4.7 Hz, 12.6 Hz), 4.22-4.15 (m, 1H), 3.71 (s, 3H), 3.59 (s, 3H), 2.34 (s, 3H); δ_C (100 MHz, $CDCl_3$) 173.1, 158.9, 143.7, 138.5, 134.4, 129.4, 129.4, 129.0, 128.5, 128.2, 127.9, 126.7, 114.1, 79.2, 56.1, 55.0, 53.1, 46.6, 21.5; IR (film): ν_{max}/cm^{-1} 596, 610, 686, 816, 837, 947, 1033, 1092, 1153, 1181, 1254, 1289, 1380, 1439, 1515, 1554, 1612; HRMS (FAB) m/z calcd. for $C_{25}H_{26}N_2O_6S$ $[M+H]^+$: 482.1512, found: 482.1512.

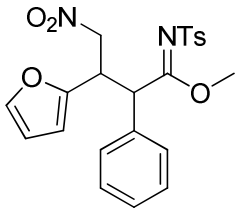
Anti isomer: NMR: δ_H (400 MHz, $CDCl_3$) 7.67 (d, 2H, *J* = 7.0 Hz), 7.57 (d, 2H, *J* = 7.9 Hz), 7.44-7.32 (m, 5H), 7.18 (d, 2H, *J* = 8.6 Hz), 6.83 (d, 2H, *J* = 8.7 Hz), 5.46 (d, 1H, *J* = 11.6 Hz), 4.51-4.45 (m, 1H), 4.29-4.24 (m, 2H), 3.77 (s, 3H), 3.52 (s, 3H), 2.37 (s, 3H); δ_C (100 MHz, $CDCl_3$) 171.2, 159.3, 143.2, 138.6, 134.5, 129.4, 129.3, 129.2, 129.0, 128.9, 128.4, 126.5, 126.0, 114.2, 78.9, 55.5, 55.1, 51.2, 46.5, 21.5; IR (film): ν_{max}/cm^{-1} 603, 683, 707, 735, 813, 949, 1033, 1092, 1155, 1182, 1254, 1289, 1313, 1344, 1379, 1439, 1514, 1554, 1596, 1612, 2953; HRMS (FAB) m/z calcd. for $C_{25}H_{26}N_2O_6S$ $[M+H]^+$: 482.1512, found: 482.1512.



Methyl 4-nitro-2-phenyl-3-*p*-tolyl-*N*-tosylbutanimidate (Table 2, entry 6): yellowish solid (58%), R_f = 0.41 (*n*-hexane/ethyl acetate = 3/1); d.r. = 57 : 43; NMR: δ_H (400 MHz, $CDCl_3$) 7.85 (d, 1H, *J* = 8.3 Hz), 7.70 (d, 1H, *J* = 7.1 Hz), 7.57 (d, 1H, *J* = 8.3 Hz), 7.45-7.30 (m, 4.5H), 7.19-7.10 (m, 3.5H), 7.05 (d, 1H, *J* = 8.1 Hz), 6.96 (d, 1H, *J* = 7.9 Hz), 5.52 (d, 0.5H, *J* = 11.8 Hz), 5.29 (d, 0.5H, *J* = 11.6 Hz), 4.96-4.90 (dd, 0.5H, *J* = 10.3 Hz, 12.6 Hz), 4.71-4.67 (dd, 0.5H, *J* = 4.6 Hz, 12.6 Hz), 4.55-4.49 (m, 0.5H), 4.34-4.26 (m, 1.5H), 3.78 (s, 1.5H), 3.52 (s, 1.5H), 2.42 (s, 1.5H), 2.37 (s, 1.5H), 2.18 (s, 1.5H), 2.04 (s, 1.5H); δ_C (100 MHz, $CDCl_3$) 173.0, 171.0, 143.6, 143.1, 138.5, 138.4, 137.7, 137.3, 134.4, 134.3, 133.4, 133.2, 129.5, 129.4, 129.3, 129.1, 129.0, 128.8, 128.4, 127.9, 127.8, 127.7, 126.6, 126.4, 79.1, 78.7, 56.0, 55.4, 52.9, 50.9, 46.8, 46.7, 21.4, 21.3, 21.0, 20.9; IR (film): ν_{max}/cm^{-1} 603, 686, 706, 736, 816, 1018, 1092, 1155, 1254, 1288, 1313, 1379, 1439, 1555, 1595, 1613, 2952; HRMS (EI) m/z calcd. for $C_{25}H_{26}N_2O_5S$ $[M+H]^+$: 466.1562, found: 466.1558.

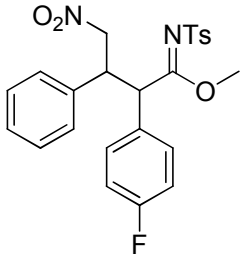


Methyl 3-(2-chlorophenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (Table 2, entry 7): yellowish solid (61%), R_f = 0.36 (*n*-hexane/ethyl acetate = 3/1), m.p. 142-143 °C; d.r. = 66 : 34; NMR: δ_H (400 MHz, $CDCl_3$) 7.82 (d, 1H, *J* = 8.4 Hz), 7.71 (d, 1H, *J* = 6.7 Hz), 7.60 (d, 1H, *J* = 8.2 Hz), 7.45-7.27 (m, 5H), 7.22-7.12 (m, 4H), 7.06-7.00 (m, 1H), 5.62 (d, 0.5H, *J* = 10.6 Hz), 5.47 (d, 0.5H, *J* = 10.9 Hz), 5.04-4.90 (m, 2.0H), 4.79-4.73 (dd, 0.5H, *J* = 4.2 Hz, 12.1 Hz), 4.40-4.34 (dd, 0.5H, *J* = 4.5 Hz, 12.6 Hz), 3.80 (s, 1.5H), 3.50 (s, 1.5H), 2.41 (s, 1.5H), 2.35 (s, 1.5H); δ_C (100 MHz, $CDCl_3$) 172.5, 170.8, 143.6, 143.3, 138.5, 138.4, 134.3, 134.3, 134.2, 133.8, 130.1, 129.4, 129.4, 129.3, 129.2, 129.2, 129.0, 129.0, 128.3, 128.1, 127.6, 127.3, 126.7, 126.4, 78.1, 56.1, 55.4, 52.2, 50.7, 43.1, 43.0, 21.5, 21.4; IR (film): ν_{max}/cm^{-1} 683, 705, 744, 761, 814, 915, 946, 975, 1017, 1037, 1091, 1152, 1187, 1254, 1289, 1378, 1438, 1479, 1495, 1554, 1610; HRMS (ESI) m/z calcd. for $C_{24}H_{23}ClN_2O_5S$ $[M+H]^+$: 487.1089, found: 487.1079.

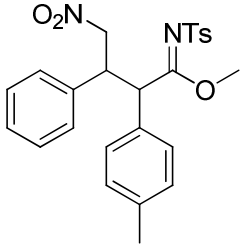


Methyl 3-(furan-2-yl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (Table 2, entry 8): yellowish solid (61%), R_f = 0.33 (*n*-hexane/ethyl acetate = 3/1); d.r. = 57 : 43; NMR: δ_H (400 MHz, $CDCl_3$) 7.78 (d, 1H, *J* = 8.3 Hz), 7.64 (d, 1H, *J* = 8.3 Hz), 7.61 (d, 1H, *J* = 6.9 Hz), 7.43-7.19 (m, 7H), 6.33 (d, 0.5H, *J* = 3.2 Hz), 6.28 (dd, 0.5H, *J* = 1.9 Hz, 3.3 Hz), 6.05 (dd, 0.5H, *J* = 1.9 Hz, 3.3 Hz), 5.92 (d, 0.5H, *J* = 3.3 Hz), 5.46 (d, 0.5H, *J* = 11.4 Hz), 5.33 (d, 0.5H, *J* = 11.3 Hz), 4.96-4.88 (dd, 0.5H, *J* = 10.2 Hz, 12.9 Hz), 4.61-4.41 (m, 2H), 4.26-4.20 (dd, 0.5H, *J* = 3.0 Hz, 12.8 Hz), 3.79 (s, 1.5H), 3.64 (s, 1.5H),

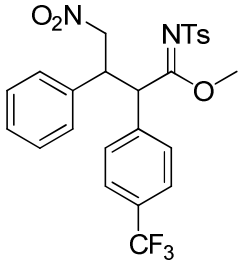
2.39 (s, 1.5H), 2.37 (s, 1H); δ_C (100 MHz, $CDCl_3$) 172.0, 170.9, 150.0, 148.9, 143.6, 143.3, 142.8, 142.5, 138.5, 138.4, 134.3, 133.8, 129.5, 129.4, 129.4, 129.2, 129.0, 128.9, 128.5, 128.1, 126.7, 126.5, 110.4, 110.1, 109.5, 108.3, 76.7, 76.0, 56.1, 55.8, 50.8, 49.6, 41.3, 40.6, 21.4, 21.4; IR (film): ν_{max}/cm^{-1} 557, 603, 686, 707, 738, 815, 947, 1015, 1092, 1156, 1259, 1289, 1317, 1377, 1439, 1495, 1556, 1595, 1613, 2952; HRMS (FAB) m/z calcd. for $C_{22}H_{22}N_2O_6S$ $[M+H]^+$: 442.1199, found: 442.1195.



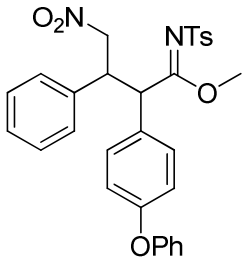
Methyl 2-(4-fluorophenyl)-4-nitro-3-phenyl-*N*-tosylbutanimidate (Table 3, entry 1): yellowish solid (67%), R_f = 0.38 (*n*-hexane/ethyl acetate = 3/1); d.r. = 61 : 39; NMR: δ_H (400 MHz, $CDCl_3$) 7.83 (d, 1H, *J* = 8.3 Hz), 7.69-7.66 (m, 1H), 7.55 (d, 1H, *J* = 8.3 Hz), 7.41-7.39 (m, 1H), 7.34-7.23 (m, 3.5H), 7.18-7.08 (m, 4.5H), 6.86-6.81 (m, 1H), 5.52 (d, 0.5H, *J* = 11.6 Hz), 5.26 (d, 0.5H, *J* = 11.7 Hz), 4.95-4.89 (dd, 0.5H, *J* = 10.1 Hz, 12.8 Hz), 4.71-4.66 (dd, 0.5H, *J* = 4.7 Hz, 12.8 Hz), 4.56-4.49 (m, 0.5H), 4.31-4.21 (m, 1.5H), 3.78 (s, 1.5H), 3.47 (s, 1.5H), 2.41 (s, 1.5H), 2.35 (s, 1.5H); δ_C (100 MHz, $CDCl_3$) 172.6, 170.7, 162.8 (d, ^1J = 247.1 Hz), 162.1 (d, ^1J = 245.9 Hz), 143.8, 143.3, 138.3, 138.3, 136.4, 136.1, 131.0 (d, ^3J = 8.1 Hz), 130.8 (d, ^3J = 8.2 Hz), 130.1 (d, ^4J = 3.4 Hz), 130.0 (d, ^4J = 3.3 Hz), 129.4, 129.2, 128.8, 128.7, 128.2, 128.1, 127.9, 126.6, 126.4, 116.3 (d, ^2J = 21.5 Hz), 115.4 (d, ^2J = 21.3 Hz), 78.9, 78.6, 56.1, 55.5, 52.2, 50.2, 47.3, 47.2, 21.4, 21.4; IR (film): ν_{max}/cm^{-1} 597, 686, 813, 848, 1091, 1153, 1226, 1290, 1380, 1510, 1553, 1611; HRMS (EI) m/z calcd. for $C_{24}H_{23}FN_2O_5S$ $[M+H]^+$: 470.1312, found: 470.1310.



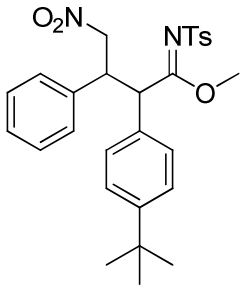
Methyl 4-nitro-3-phenyl-2-*p*-tolyl-*N*-tosylbutanimidate (Table 3, entry 2): yellowish solid (64%), R_f = 0.42 (*n*-hexane/ethyl acetate = 3/1); d.r. = 59 : 41; NMR: δ_H (400 MHz, $CDCl_3$) 7.84 (d, 1H, *J* = 8.3 Hz), 7.59-7.55 (m, 1.5H), 7.43-7.41 (m, 1H), 7.33-7.07 (m, 8.5H), 6.96 (d, 1H, *J* = 8.0 Hz), 5.47 (d, 0.5H, *J* = 11.5 Hz), 5.25 (d, 0.5H, *J* = 11.6 Hz), 4.96-4.90 (dd, 0.5H, *J* = 10.3 Hz, 12.8 Hz), 4.70-4.66 (dd, 0.5H, *J* = 4.6 Hz, 12.7 Hz), 4.56-4.50 (m, 0.5H), 4.34-4.27 (m, 1.5H), 3.77 (s, 1.5H), 3.47 (s, 1.5H), 2.41 (s, 1.5H), 2.35 (s, 1.5H), 2.33 (s, 1.5H), 2.18 (s, 1.5H); δ_C (100 MHz, $CDCl_3$) 173.2, 171.2, 143.6, 143.1, 138.7, 138.4, 137.6, 136.7, 136.4, 131.2, 131.0, 130.0, 129.4, 129.1, 128.8, 128.8, 128.6, 128.1, 128.0, 127.7, 126.6, 126.3, 79.0, 78.7, 56.0, 55.4, 52.5, 50.6, 47.1, 21.4, 21.4, 21.0, 20.9; IR (film): ν_{max}/cm^{-1} 599, 686, 703, 816, 836, 948, 1018, 1092, 1154, 1187, 1255, 1289, 1313, 1379, 1439, 1495, 1513, 1555, 1601, 1619, 2951; HRMS (EI) m/z calcd. for $C_{25}H_{26}N_2O_5S$ $[M+H]^+$: 466.1562, found: 466.1558.



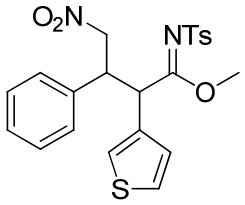
Methyl 4-nitro-3-phenyl-*N*-tosyl-2-(4-(trifluoromethyl)phenyl)butanimidate (Table 3, entry 3): yellowish solid (73%), m.p. 112-113 °C, R_f = 0.42 (*n*-hexane/ethyl acetate = 3/1); d.r. = 64 : 36; NMR: δ_H (400 MHz, $CDCl_3$) 7.86-7.82 (m, 2H), 7.68 (d, 1H, *J* = 8.2 Hz), 7.56-7.41 (m, 3.5H), 7.37-7.24 (m, 2.5H), 7.19-7.09 (m, 4H), 5.61 (d, 0.5H, *J* = 11.9 Hz), 5.36 (d, 0.5H, *J* = 11.7 Hz), 4.97-4.92 (dd, 0.5H, *J* = 10.1 Hz, 12.9 Hz), 4.74-4.69 (dd, 0.5H, *J* = 4.7 Hz, 12.8 Hz), 4.58-4.52 (dd, 0.5H, *J* = 10.7 Hz, 12.4 Hz), 4.36-4.22 (m, 1.5H), 3.79 (s, 1.5H), 3.49 (s, 1.5H), 2.41 (s, 1.5H), 2.35 (s, 1.5H); δ_C (100 MHz, $CDCl_3$) 171.9, 170.0, 143.9, 143.5, 138.3, 138.1, 136.1, 135.8, 131.0 (q, ^2J = 32.3 Hz), 130.5, 129.8, 129.7, 129.6, 129.5, 129.2, 128.9, 128.9, 128.4, 128.1, 127.9, 126.7, 126.4, 126.3 (q, ^4J = 3.7 Hz), 125.3 (q, ^4J = 3.6 Hz), 123.7 (q, ^1J = 270.5 Hz), 78.8, 78.4, 56.3, 55.7, 52.8, 50.7, 47.0, 21.4, 21.4; IR (film): ν_{max}/cm^{-1} 559, 686, 704, 815, 853, 946, 1018, 1070, 1091, 1128, 1155, 1257,1327, 1380, 1556, 1609; HRMS (EI) m/z calcd. for $C_{25}H_{23}F_3N_2O_5S$ $[M+H]^+$: 520.1280, found: 520.1284.



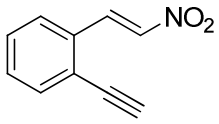
Methyl 4-nitro-2-(4-phenoxyphenyl)-3-phenyl-*N*-tosylbutanimidate (Table 3, entry 4): yellow solid (74%), m.p. 129-130 °C, R_f = 0.41 (*n*-hexane/ethyl acetate = 3/1); d.r. = 57 : 43; NMR: δ_H (400 MHz, $CDCl_3$) 7.85 (d, 1H, *J* = 8.2 Hz), 7.64 (d, 1H, *J* = 8.6 Hz), 7.57 (d, 1H, *J* = 8.3 Hz), 7.42-7.24 (m, 6H), 7.19-7.02 (m, 7H), 6.88 (d, 1H, *J* = 7.7 Hz), 6.79 (d, 1H, 8.6 Hz), 5.50 (d, 0.5H, *J* = 11.8 Hz), 5.25 (d, 0.5H, *J* = 11.6 Hz), 4.96-4.91 (dd, 0.5H, *J* = 10.2 Hz, 12.8 Hz), 4.71-4.67 (dd, 0.5H, *J* = 4.6 Hz, 12.8 Hz), 4.57-4.52 (dd, 0.5H, *J* = 11.0 Hz, 12.4 Hz), 4.37-4.24 (m, 1.5H), 3.80 (s, 1.5H), 3.49 (s, 1.5H), 2.42 (s, 1.5H), 2.36 (s, 1.5H); δ_C (100 MHz, $CDCl_3$) 172.9, 171.0, 158.0, 156.9, 156.6, 156.2, 143.7, 143.2, 138.5, 138.4, 136.6, 136.3, 130.7, 130.4, 129.8, 129.6, 129.4, 129.2, 128.8, 128.7, 128.5, 128.2, 128.1, 128.0, 127.8, 126.7, 126.4, 123.9, 123.4, 119.5, 118.9, 118.5, 78.9, 78.7, 56.1, 55.4, 52.4, 50.3, 47.4, 47.2, 21.5, 21.4; IR (film): ν_{max}/cm^{-1} 598, 686, 755, 815, 845, 874, 947, 1017, 1092, 1153, 1242, 1288, 1313, 1378, 1438, 1456, 1488, 1506, 1556, 1589, 1617, 1699; HRMS (EI) m/z calcd. for $C_{30}H_{28}N_2O_6S$ $[M+H]^+$: 544.1668, found: 544.1664.



Methyl 2-(4-*tert*-butylphenyl)-4-nitro-3-phenyl-*N*-tosylbutanimidate (Table 3, entry 5): yellowish solid (56%), R_f = 0.40 (*n*-hexane/ethyl acetate = 3/1); d.r. = 63 : 37; NMR: δ_H (400 MHz, $CDCl_3$) 7.82 (d, 1H, *J* = 8.3 Hz), 7.59 (d, 1H, *J* = 8.3 Hz), 7.54 (d, 1H, *J* = 8.3 Hz), 7.43-7.23 (m, 5H), 7.17-7.06 (m, 5H), 5.47 (d, 0.5H, *J* = 11.6 Hz), 5.25 (d, 0.5H, *J* = 11.5 Hz), 4.96-4.90 (dd, 0.5H, *J* = 10.3 Hz, 12.7 Hz), 4.69-4.65 (dd, 0.5H, *J* = 4.6 Hz, 12.7 Hz), 4.56-4.49 (m, 0.5H), 4.34-4.26 (m, 1.5H), 3.77 (s, 1.5H), 3.47 (s, 1.5H), 2.40 (s, 1.5H), 2.34 (s, 1.5H), 1.33 (s, 4.5H), 1.20 (s, 4.5H); δ_C (100 MHz, $CDCl_3$) 173.2, 171.2, 151.8, 150.7, 143.6, 143.1, 138.6, 138.5, 136.7, 136.5, 131.1, 131.0, 129.4, 129.1, 128.9, 128.8, 128.6, 128.2, 128.1, 128.0, 127.7, 126.7, 126.4, 126.3, 125.3, 79.0, 78.8, 56.0, 55.4, 52.6, 50.5, 47.2, 47.1, 34.5, 34.3, 31.2, 31.1, 21.5, 21.4; IR (film): ν_{max}/cm^{-1} 592, 619, 686, 704, 738, 815, 847, 948, 1018, 1092, 1155, 1185, 1254, 1289, 1314, 1335, 1379, 1438, 1456, 1496, 1556, 1596, 1620, 2868, 2904, 2952, 2967, 3033; HRMS (EI) m/z calcd. for $C_{28}H_{32}N_2O_5S$ $[M+H]^+$: 508.2032, found: 508.2037.

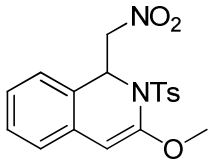


Methyl 4-nitro-3-phenyl-2-(thiophen-3-yl)-*N*-tosylbutanimidate (Table 3, entry 6): yellowish solid (69%), m.p. 135-136 °C, R_f = 0.40 (*n*-hexane/ethyl acetate = 3/1); d.r. = 60 : 40; NMR: δ_H (400 MHz, $CDCl_3$) 7.82 (d, 1H, *J* = 8.1 Hz), 7.56 (d, 1H, *J* = 8.3 Hz), 7.39-7.36 (m, 1H), 7.33-7.22 (m, 3H), 7.20-7.07 (m, 5H), 7.00-6.99 (m, 1H), 5.65 (d, 0.5H, *J* = 11.8 Hz), 5.38 (d, 0.5H, *J* = 11.4 Hz), 4.94-4.88 (m, 0.5H), 4.68-4.64 (m 0.5H), 4.57-4.52 (m, 0.5H), 4.38-4.34 (m, 0.5H), 4.31-4.19 (m, 1H), 3.78 (s, 1.5H), 3.47 (s, 1.5H), 2.40 (s, 1.5H), 2.35 (s, 1.5H); δ_C (100 MHz, $CDCl_3$) 172.6, 170.7, 143.7, 143.2, 138.4, 138.2, 136.4, 136.3, 134.3, 134.1, 129.4, 129.2, 128.8, 128.7, 128.2, 128.0, 127.9, 127.8, 127.3, 127.2, 126.9, 126.6, 126.4, 125.6, 125.5, 124.8, 78.7, 78.6, 56.0, 55.4, 48.6, 47.4, 47.1, 46.5, 21.5, 21.4; IR (film): ν_{max}/cm^{-1} 598, 686, 704, 735, 774, 816, 952, 1018, 1092, 1150, 1158, 1185, 1233, 1268, 1315, 1379, 1439, 1456, 1496, 1554, 1596, 1620, 2951, 3032, 3108; HRMS (EI) m/z calcd. for $C_{22}H_{22}N_2O_5S_2$ $[M+H]^+$: 458.0970, found: 458.0973.



(*E*)-1-ethynyl-2-(2-nitrovinyl)benzene:[2] A flame-dried flask equipped with a magnetic stirring bar was charged with 2-ethynylbenzaldehyde (990 mg, 7.6 mmol) and nitromethane (2 mL, 38.1 mmol) under a N_2 atmosphere. Triethylamine (211 µL, 1.5 mmol) was then slowly added and the mixture was stirred at room temperature. After 16 h the mixture was evaporated and directly subjected to column chromatography (86%, R_f = 0.29, *n*-hexane/ethyl acetate = 5/1). To the resulting Henry-product (850 mg, 4.4 mmol) in CH_2Cl_2 (0.5 M) was slowly added MsCl (413 µL, 5.3 mmol) and triethylamine (1.5 mL, 11.1 mmol). Water was added after 24 h and the aqueous phase was extracted with CH_2Cl_2 (3 x). The combined organic phases were then washed with 1N HCl, dried over $MgSO_4$, filtered and concentrated *in vacou*. The crude residue was purified by flash column chromatography to give desired product as a yellow solid (80%). R_f = 0.34 (*n*-hexane/ethyl acetate = 10/1); NMR: δ_H (400 MHz, $CDCl_3$) 8.45 (d, 1H, *J* = 13.7 Hz), 7.73 (d, 1H, *J* = 13.7 Hz), 7.63-7.56 (m, 2H), 7.48-7.39 (m, 2H), 3.53 (s, 1H); δ_C (100 MHz, $CDCl_3$) 138.3, 136.5, 133.9, 131.7, 131.3, 129.2, 127.3, 123.8, 84.6,

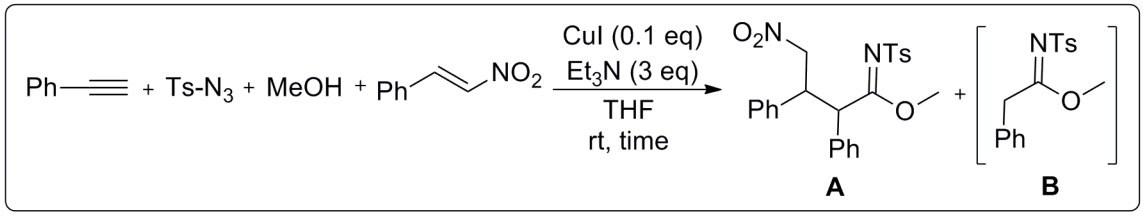
80.4; IR (film) ν_{max}/cm^{-1} 604, 646, 691, 758, 847, 965, 1212, 1257, 1283, 1348, 1477, 1500, 1517, 1593, 1629, 3268; HRMS (EI) m/z calcd. for $C_{10}H_7NO_2$ $[M+H]^+$: 173.0477, found: 173.0480.



3-Methoxy-1-(nitromethyl)-2-tosyl-1,2-dihydroisoquinoline (Scheme 2, compound 6): To a mixture of CuI (9.5 mg, 0.05 mmol), *p*-toluenesulfonyl azide (118.3 mg, 0.60 mmol) and (*E*)-1-ethynyl-2-(2-nitrovinyl)benzene (87 mg, 0.50 mmol) in THF (1.5 mL) was slowly added methanol (101 µL, 2.5 mmol) and triethylamine (208 µL, 1.5 mmol) at room temperature under a N_2 atmosphere. After 24 h, the reaction mixture was diluted with CH_2Cl_2 (3 mL) and quenched with a sat. $NHCl_4$-solution (3 mL) and a 1N HCl-solution (3 mL). The mixture was stirred for an additional 30 minutes and then the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 6 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography using silica gel with *n*-hexane/ethyl acetate = 5/1 as eluent to afford the desired product as a white solid (45%), R_f = 0.26 (*n*-hexane/ethyl acetate = 3/1); NMR: δ_H (400 MHz, $CDCl_3$) 7.56 (d, 2H, *J* = 8.4 Hz), 7.24-7.10 (m, 5H), 6.96 (d, 1H, *J* = 7.6 Hz), 6.25-6.21 (dd, 1H, *J* = 5.2 Hz, 10.0 Hz), 5.49 (s, 1H), 4.50-4.45 (dd, 1H, *J* = 10.0 Hz, *J* = 12.5 Hz), 4.31-4.27 (dd, 1H, *J* = 5.1 Hz, *J* = 12.5 Hz), 3.73 (s, 3H), 2.32 (s, 3H); δ_C (100 MHz, $CDCl_3$) 149.7, 144.1, 136.2, 131.4, 129.1, 129.0, 127.6, 126.2, 125.7, 125.5, 124.9, 90.1, 75.8, 57.5, 56.4, 21.5; IR (film): ν_{max}/cm^{-1} 540, 621, 682, 755, 814, 970, 1011, 1088, 1166, 1197, 1245, 1269, 1289, 1354, 1380, 1490, 1556, 1598, 1641; HRMS (FAB) m/z calcd. for $C_{18}H_{18}N_2O_5S$ $[M+H]^+$: 374.0936, found: 374.0934.

Reaction profile for the four-component reaction. To a mixture of CuI (3.8 mg, 0.02 mmol) and *trans*-β-nitrostyrene (30.1 mg, 0.20 mmol) in THF (0.6 mL) was slowly added phenylacetylene (26.9 µL, 0.24 mmol), *p*-toluenesulfonyl azide (36.4 µL, 0.24 mmol), methanol (40.6 µL, 1.00 mmol) and triethylamine (84.0 µL, 0.60 mmol) at room temperature under an N_2 atmosphere (Scheme S1).

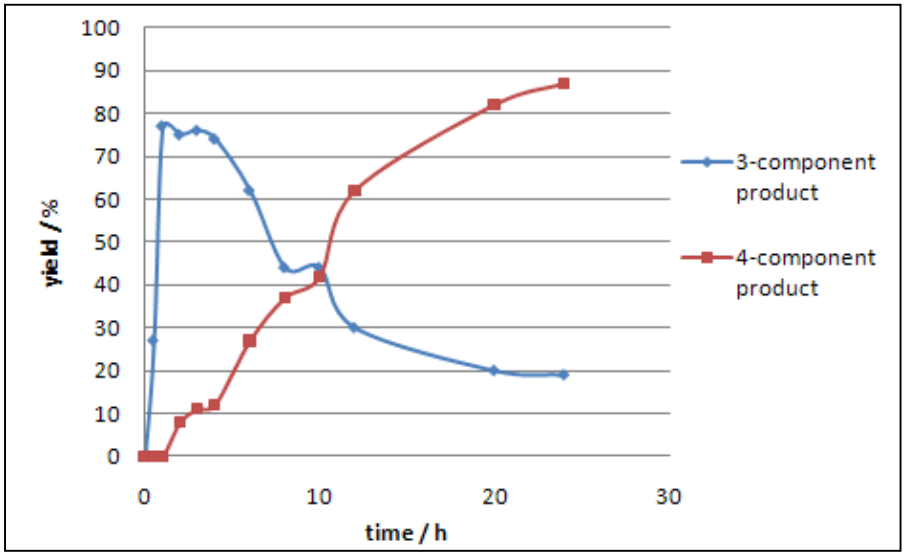
Scheme S1



After various reaction times, the reaction mixture was diluted with CH_2Cl_2, quenched with sat. NH_4Cl and 1N HCl, and stirred for an additional 10 min. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

The yield of the reaction was monitored by ^1H NMR using an internal standard (1,1,2,2-tetrachloroethane) in the periods of 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 20 h and 24 h. The results are presented in Figure S1. It was found that the three-component product **B** was observed prior to the four-component product **A**.

Figure S1

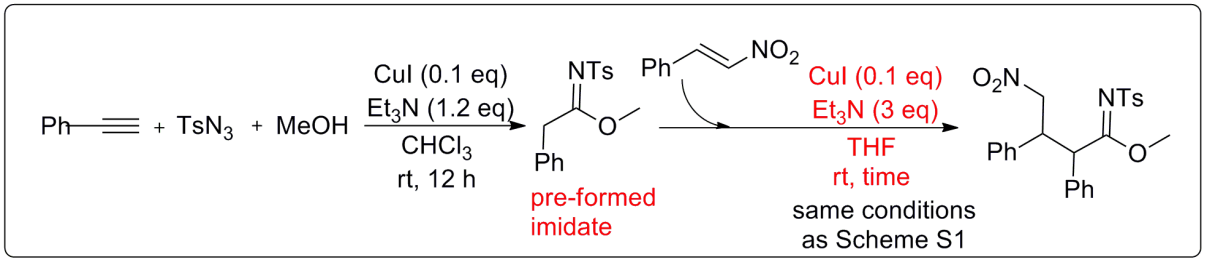


Time (h)	3-C pdt (%)	4-C pdt (%)
0	0	0
0.5	27	0
1	77	0
2	75	8
3	76	11
4	74	12
6	62	27
8	44	37
10	44	42
12	30	62
20	20	82
24	19	87

Reaction profile for the reaction of *trans*-β-nitrostyrene with pre-formed imidate. Preparation of pre-formed imidate: To a mixture of CuI (0.190 g, 1.0 mmol) in $CHCl_3$ (20 mL) was slowly added phenylacetylene (1.1 mL, 10 mmol), *p*-toluenesulfonyl azide (1.8 mL, 12 mmol), methanol (0.5 mL, 12 mmol) and triethylamine (1.7mL, 12 mmol) at room temperature under an N_2 atmosphere. After 12 h, the reaction mixture was diluted with CH_2Cl_2, quenched with sat. NH_4Cl-solution, and stirred for an additional 30 min. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography using silica gel with *n*-hexane/ethyl acetate = 5/1 as eluent to afford the desired product.

Synthesis of four-component product from pre-formed imidate: To a mixture of CuI (3.8 mg, 0.02 mmol), *trans*-β-nitrostyrene (30.1 mg, 0.20 mmol), and imidate (72.8mg, 0.24mmol) in THF (0.6 mL) was slowly added triethylamine (84.0 μL, 0.60 mmol) at room temperature under an N_2 atmosphere (Scheme S2).

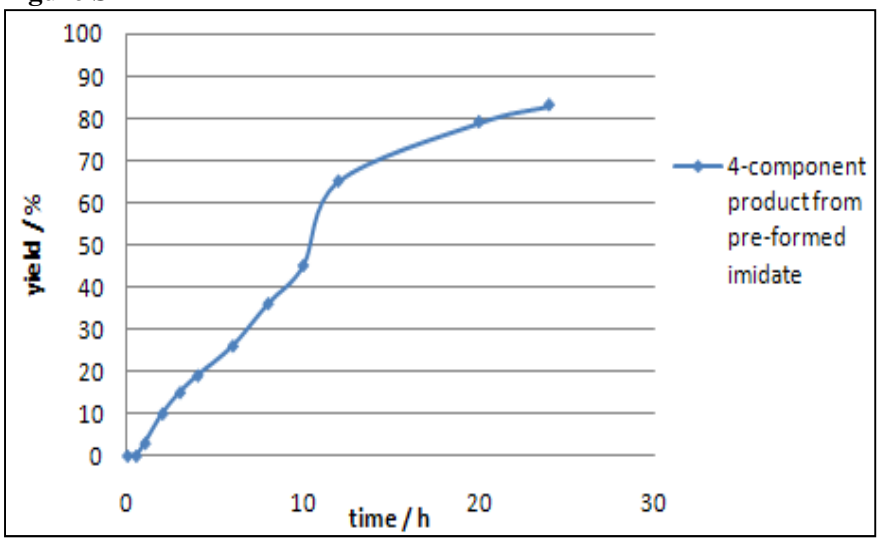
Scheme S2



After various reaction times, the reaction mixture was diluted with CH_2Cl_2, quenched with sat. NH_4Cl-solution and 1N HCl-solution, and stirred for an additional 10 min. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

The yield of the reaction was monitored by ^{1}H NMR using an internal standard (1,1,2,2-tetrachloroethane) in the periods of 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 20 h and 24 h. The results are presented in Figure S2.

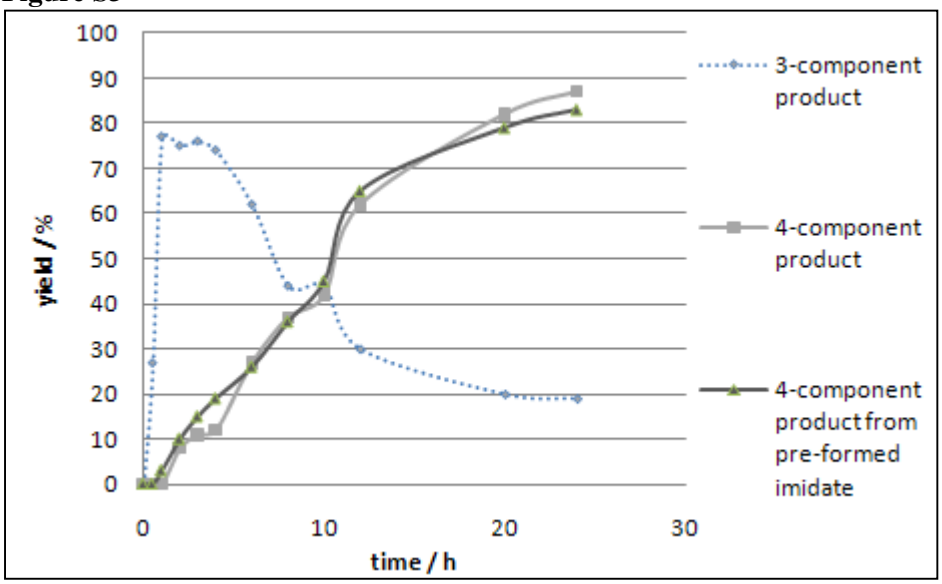
Figure S2



Time (h)	4-C pdt from pre-formed imidate (%)
0	0
0.5	0
1	3
2	10
3	15
4	19
6	26
8	36
10	45
12	65
20	79
24	83

It was observed that the rate of product formation from pre-formed imidate is similar to that of the one-pot, four-component reaction (Figure S3).

Figure S3



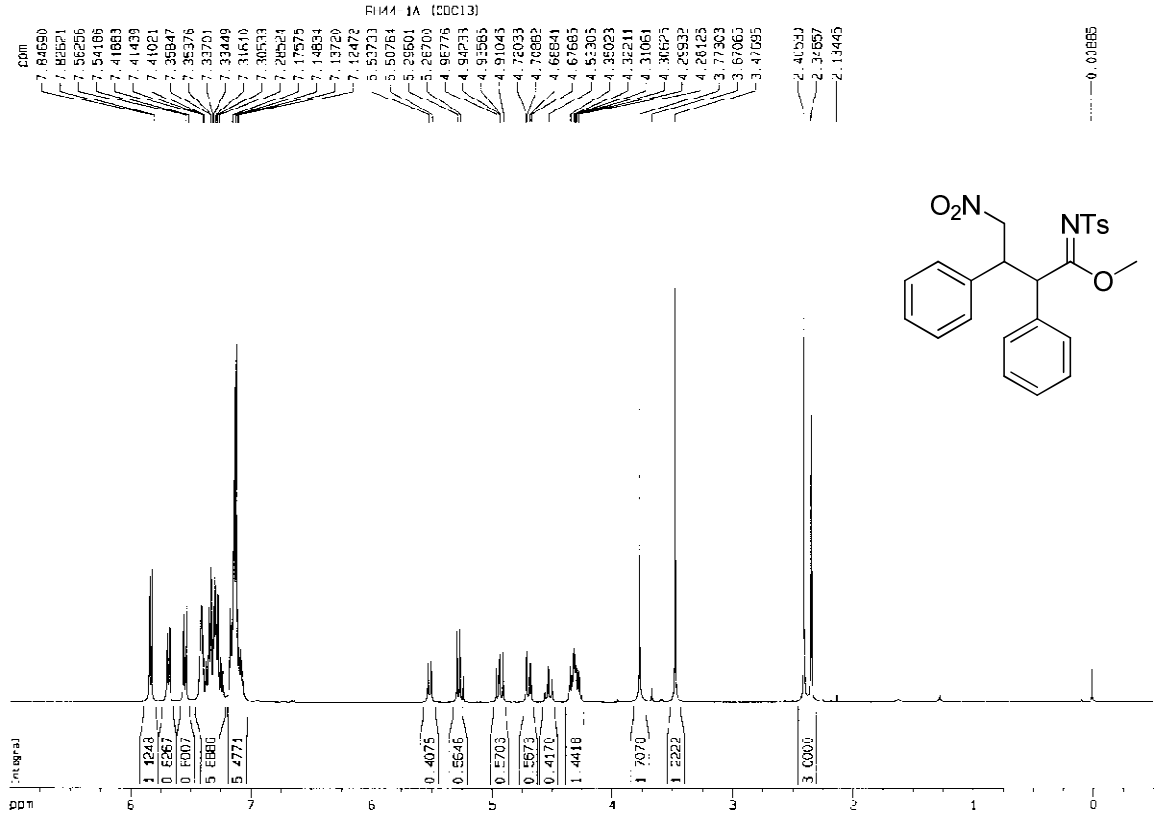
References

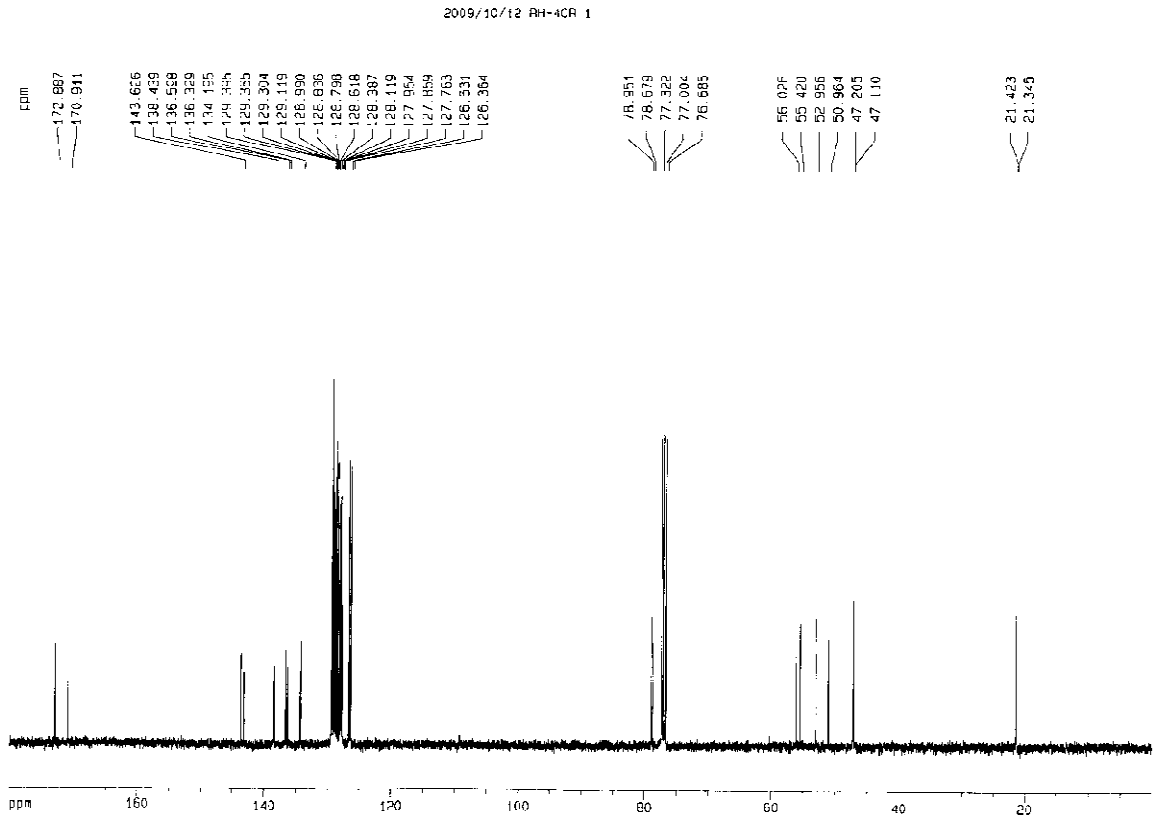
1 TsN_3 was prepared according to: A. Pollex and M. Hiersemann, *Org. Lett.*, 2005, **7**, 5705.

2 This compound was reported but no data were given: B. Tan, X. Zhang, P. Juan Chua and G. Zhong, *Chem. Commun.*, 2009, 779.

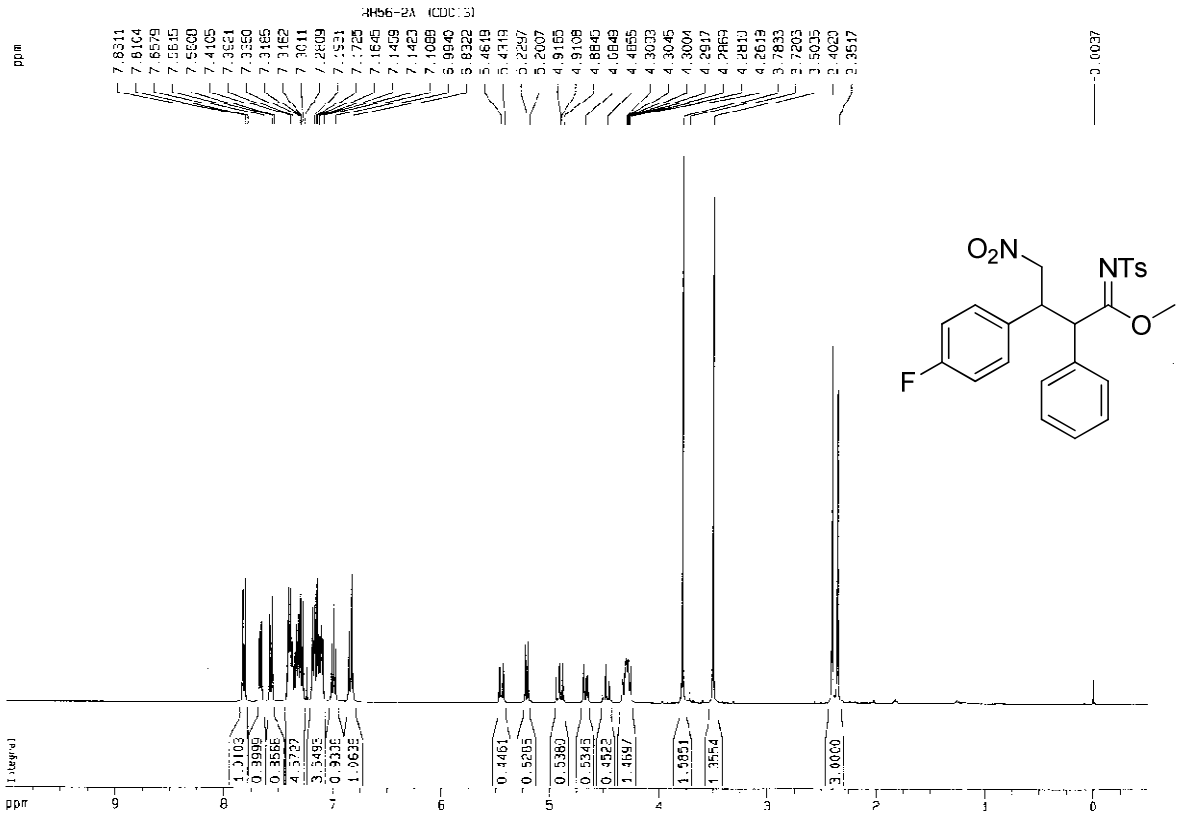
Copies of ^{1}H and ^{13}C NMR Spectra of Compounds Obtained in this Study

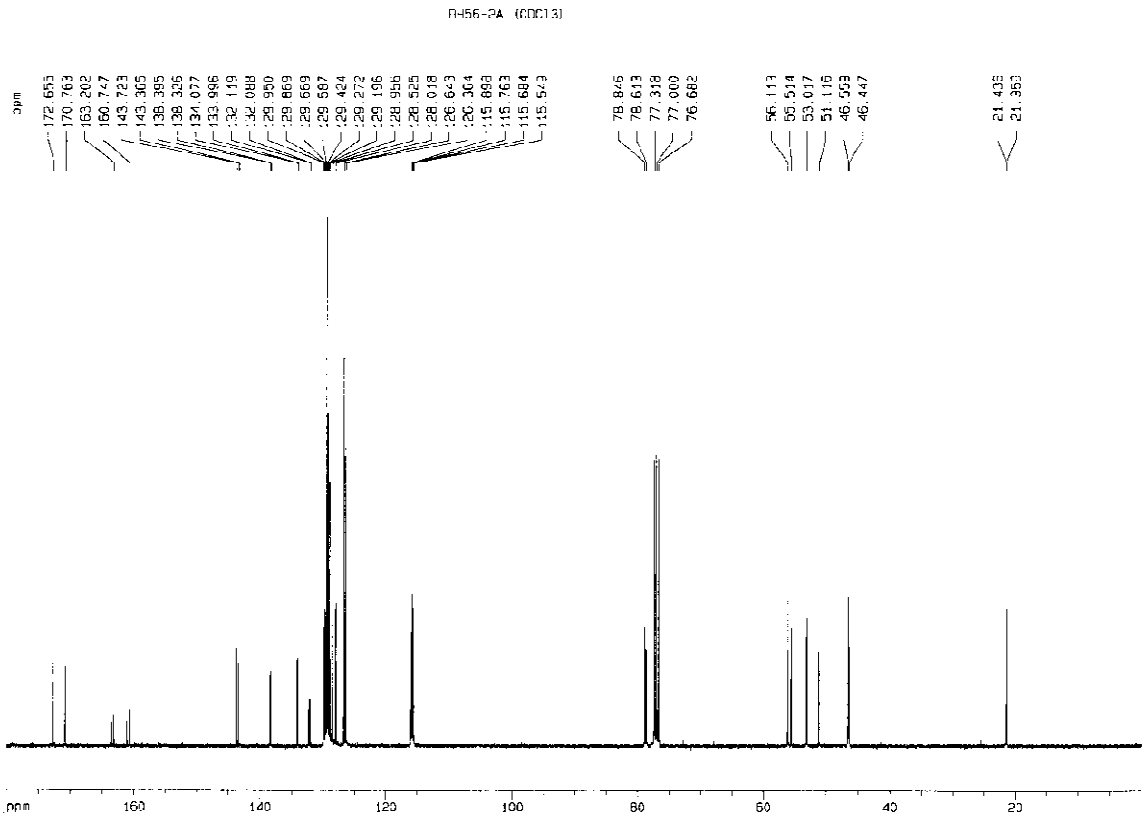
Methyl 4-nitro-2,3-diphenyl-*N*-tosylbutanimidate (Table 2, entry 1)



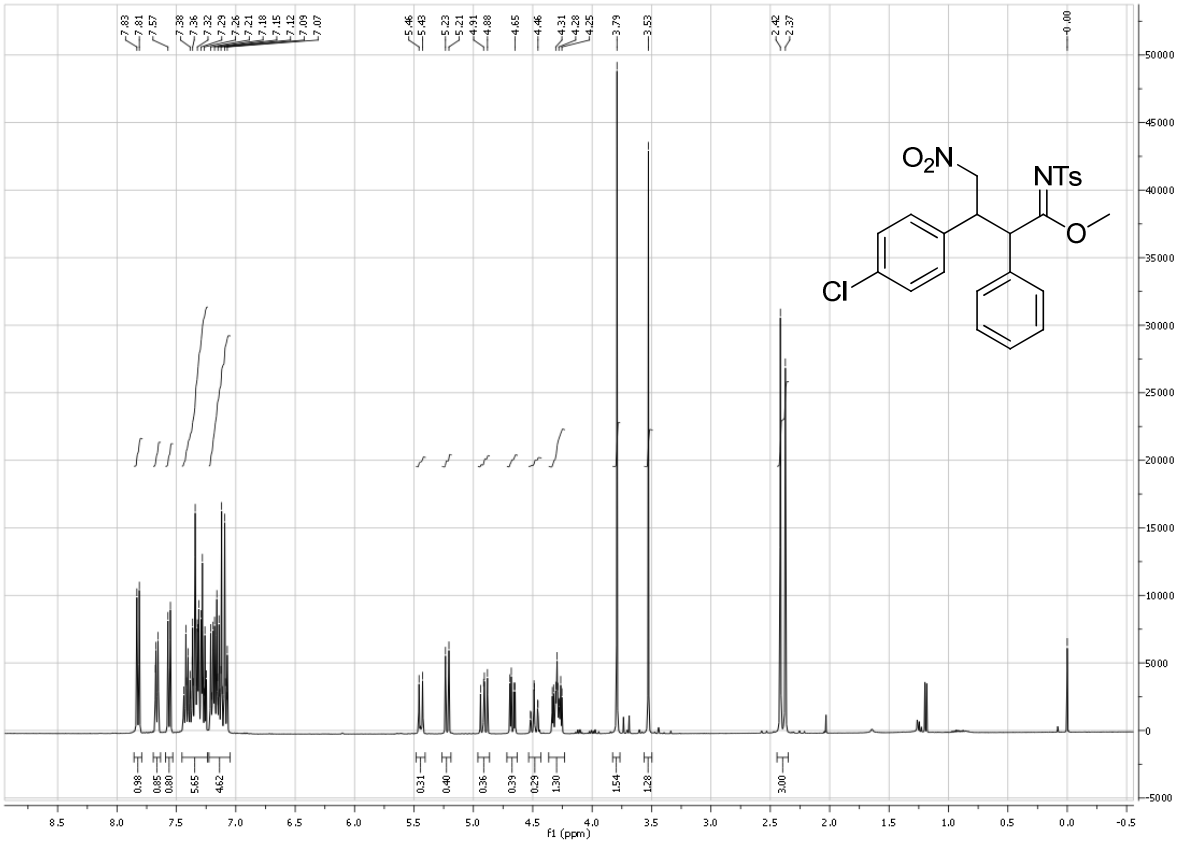


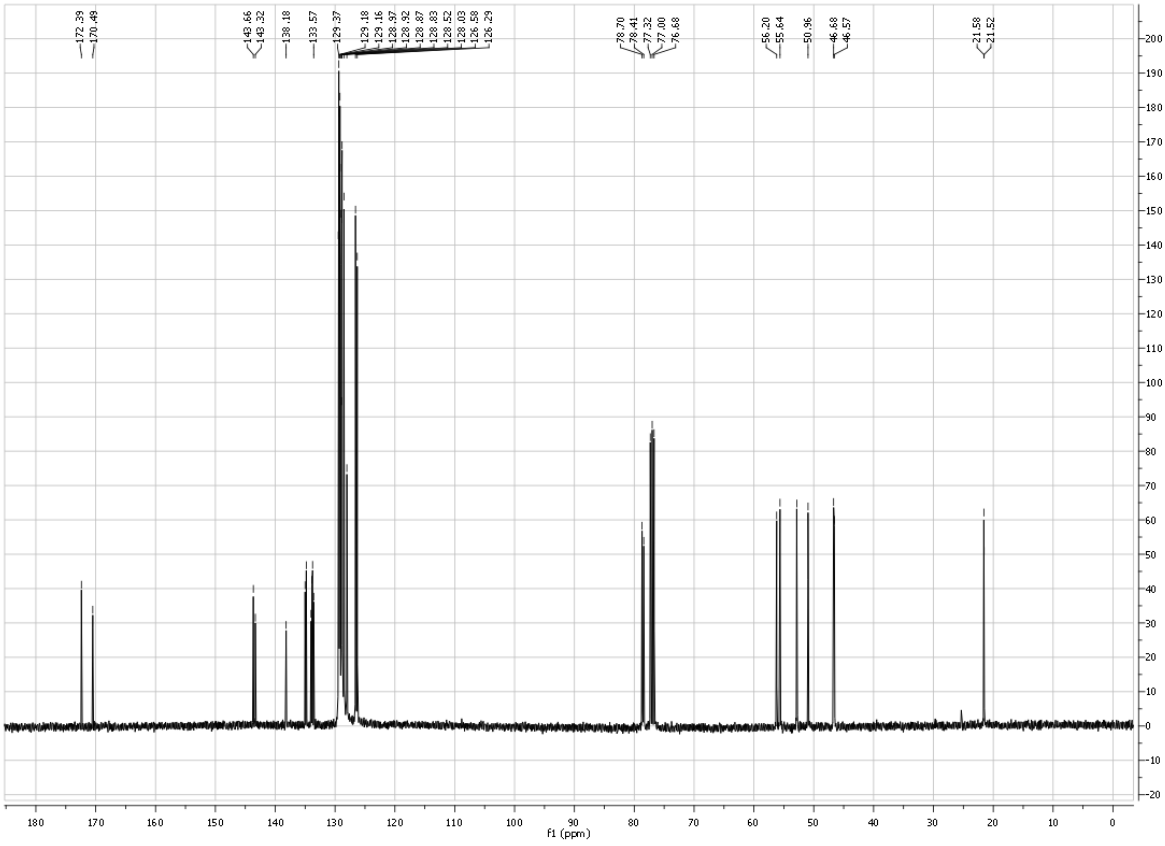
Methyl 3-(4-fluorophenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (Table 2, entry 2)



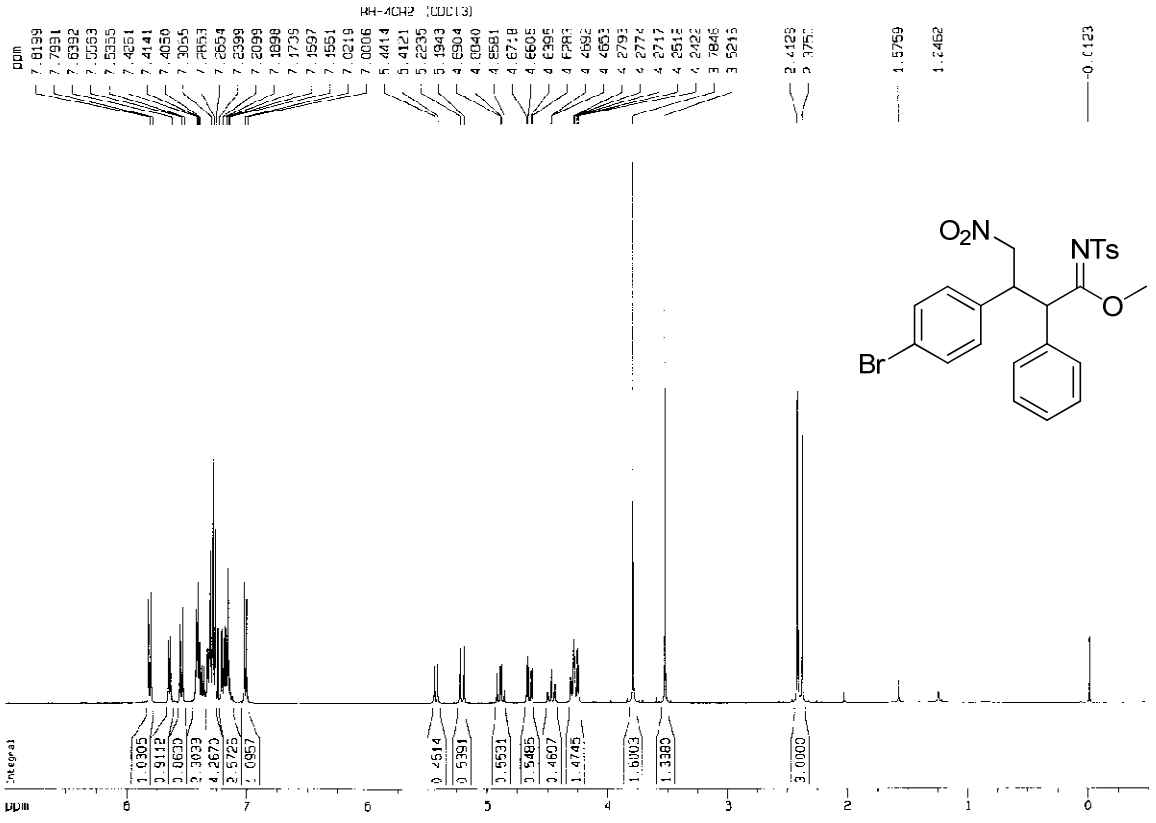


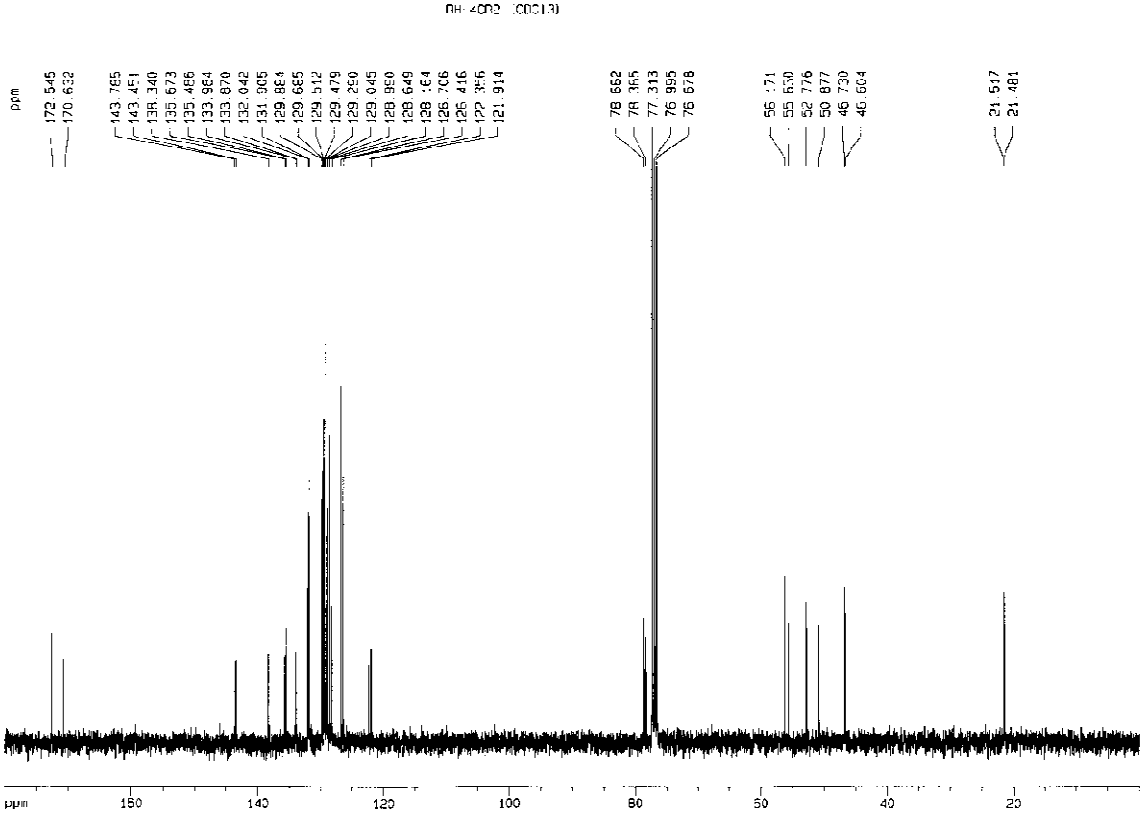
Methyl 3-(4-chlorophenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (Table 2, entry 3)



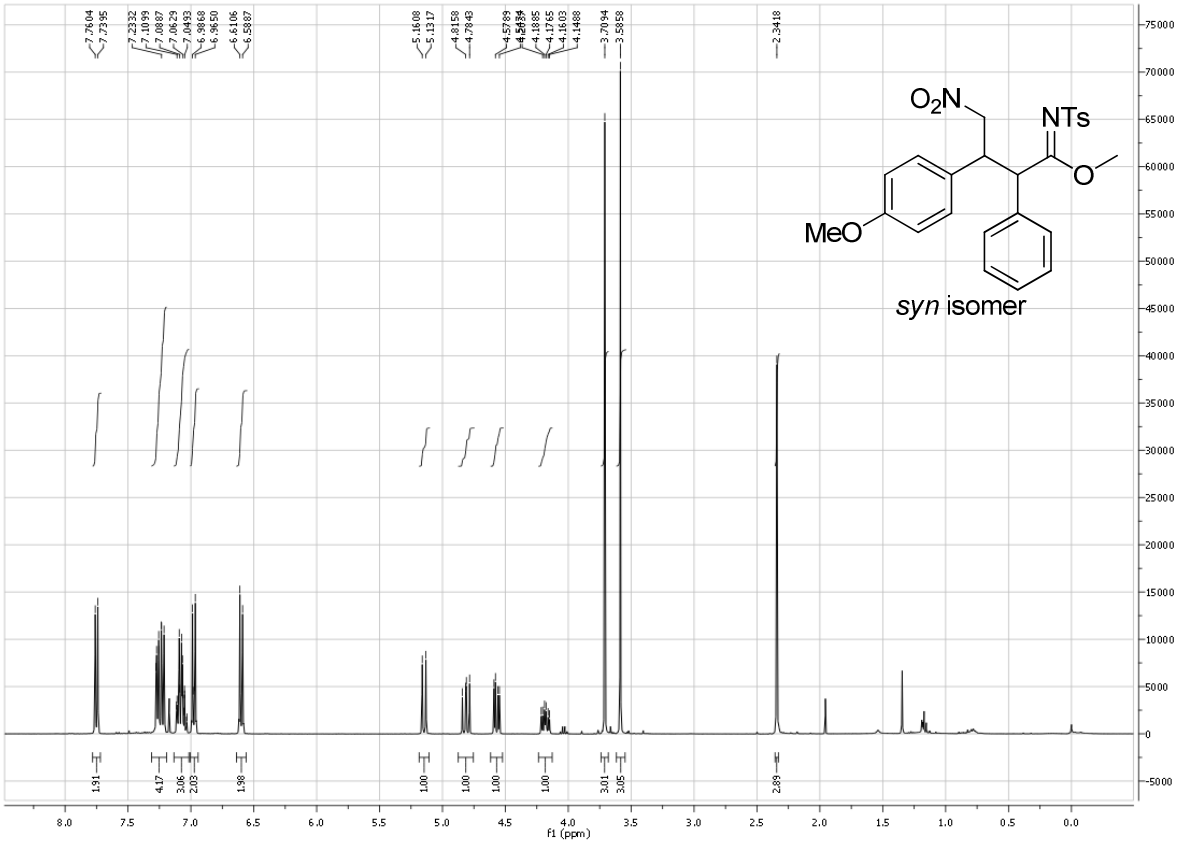


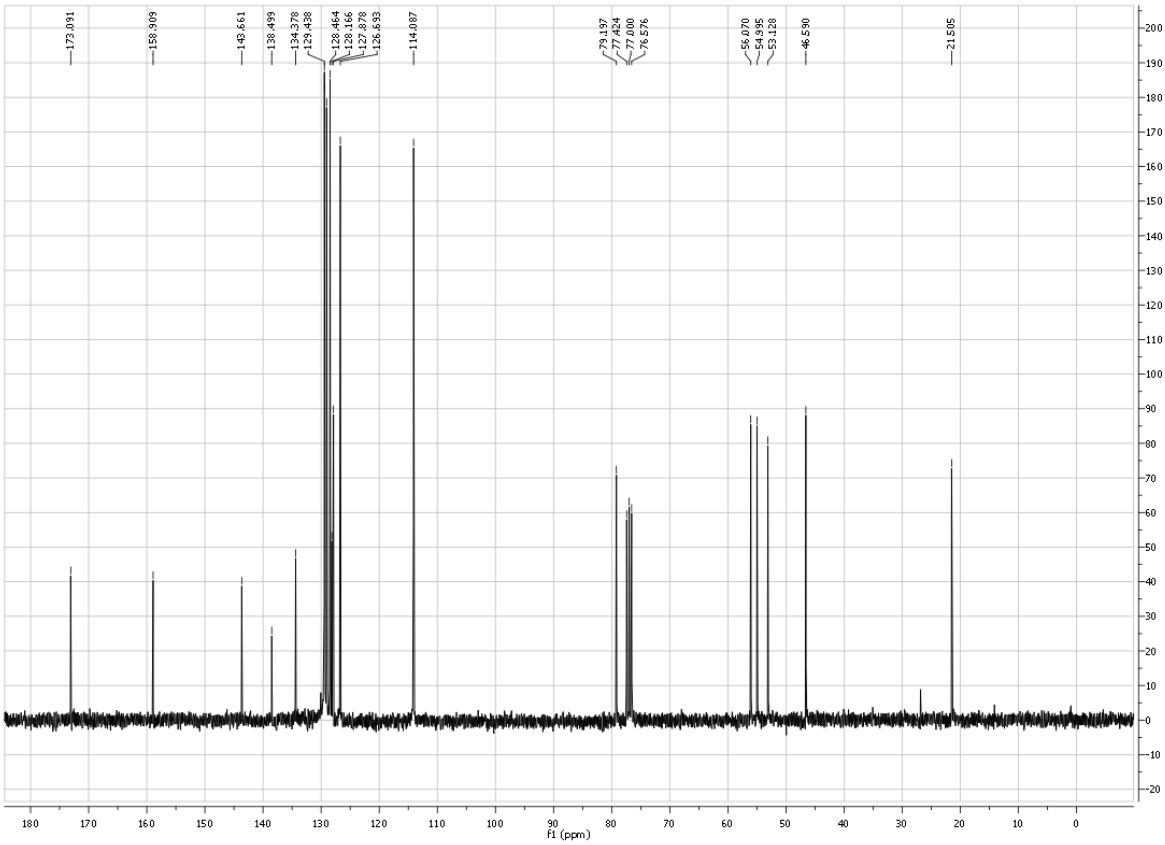
Methyl 3-(4-bromophenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (Table 2, entry 4)

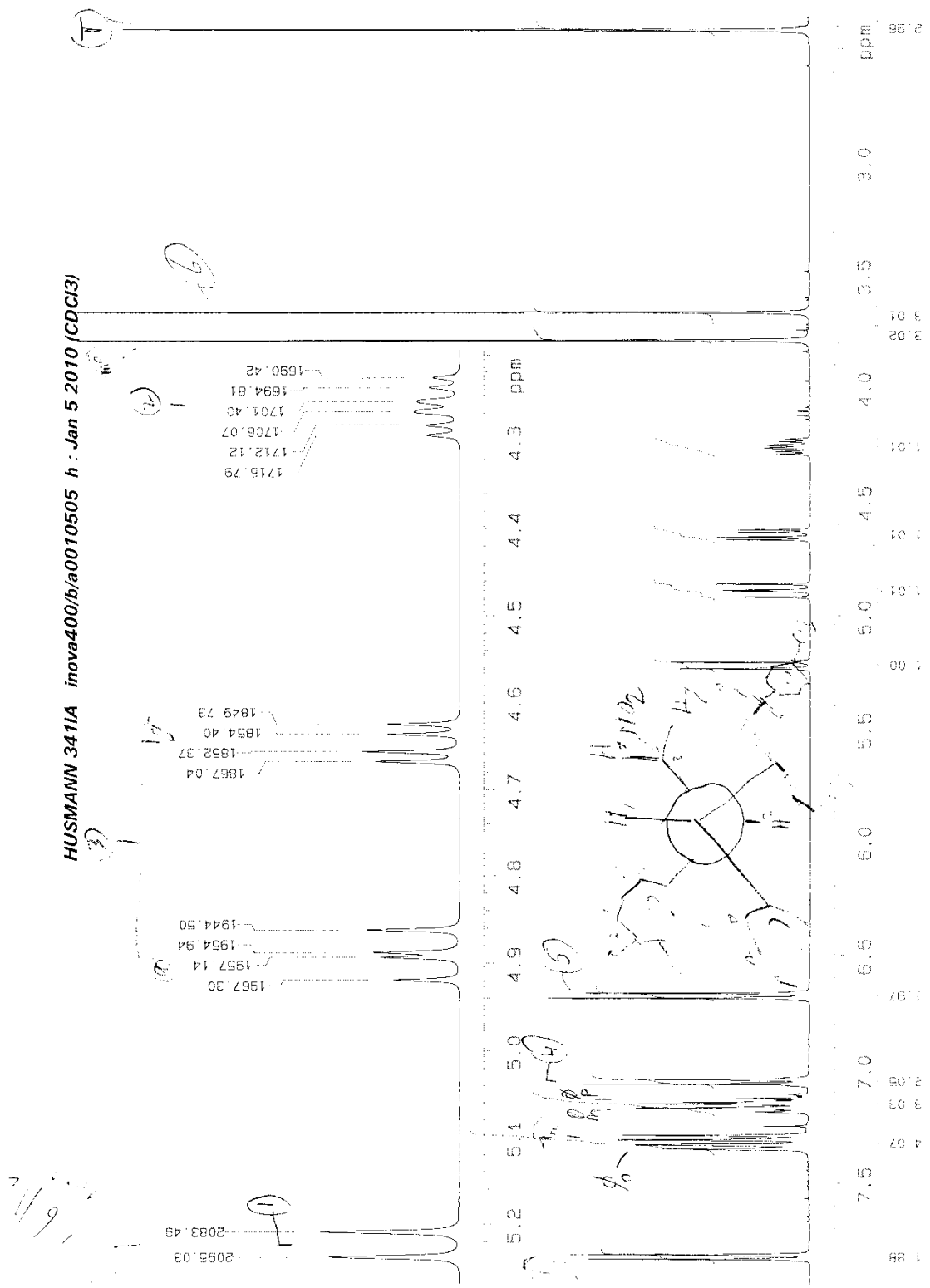




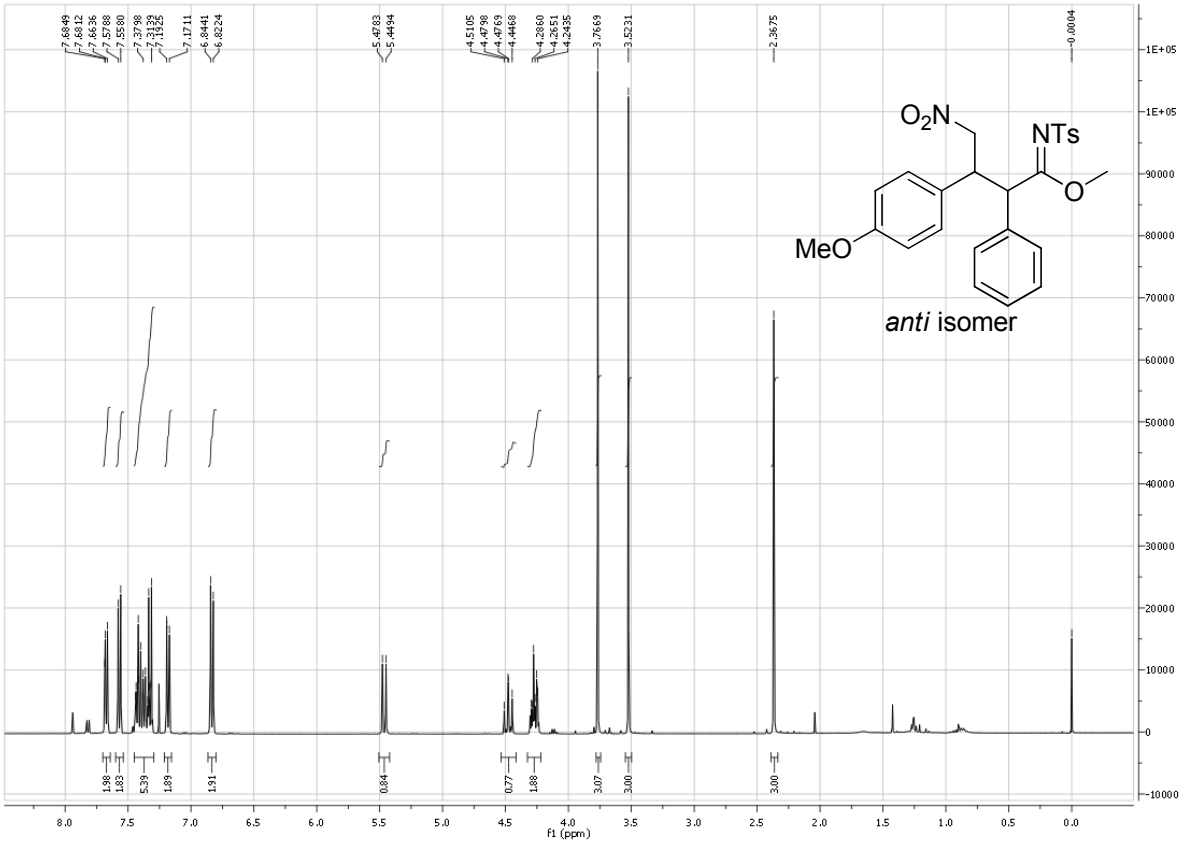
syn Methyl 3-(4-methoxyphenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (Table 2, entry 5)

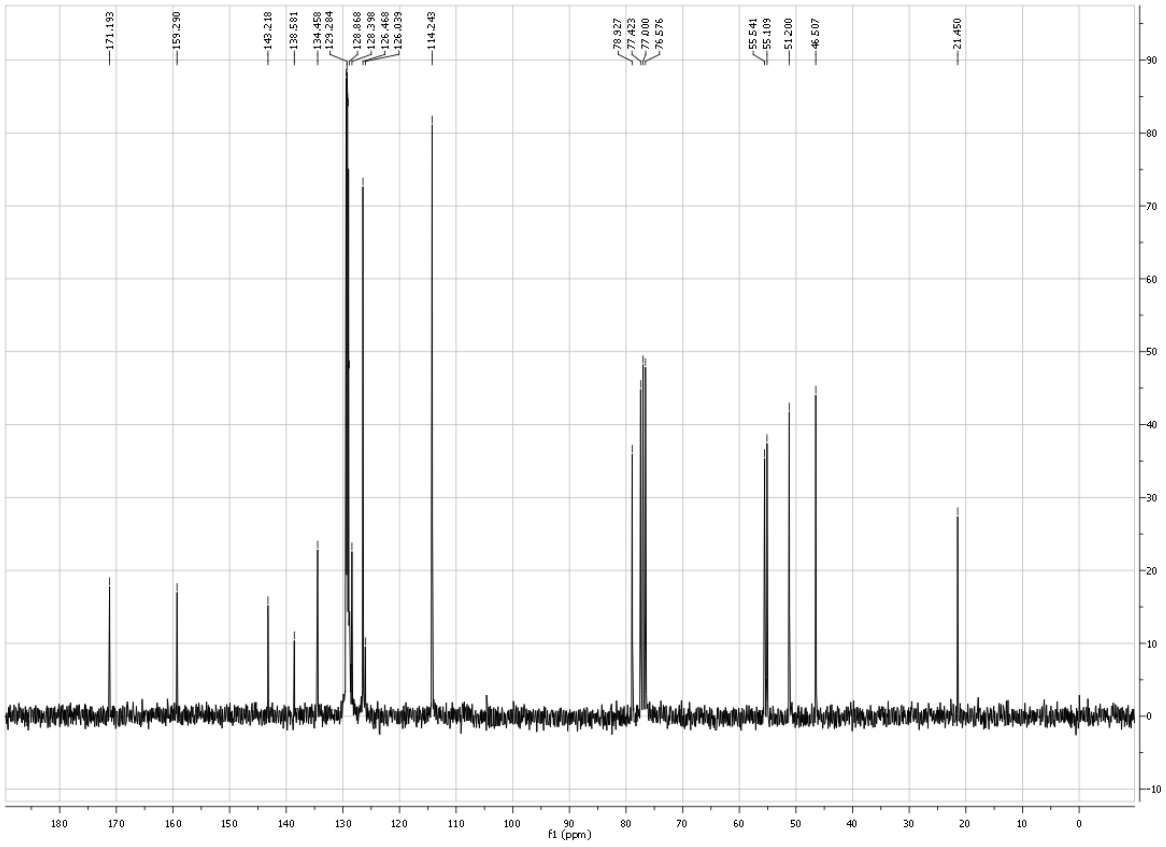


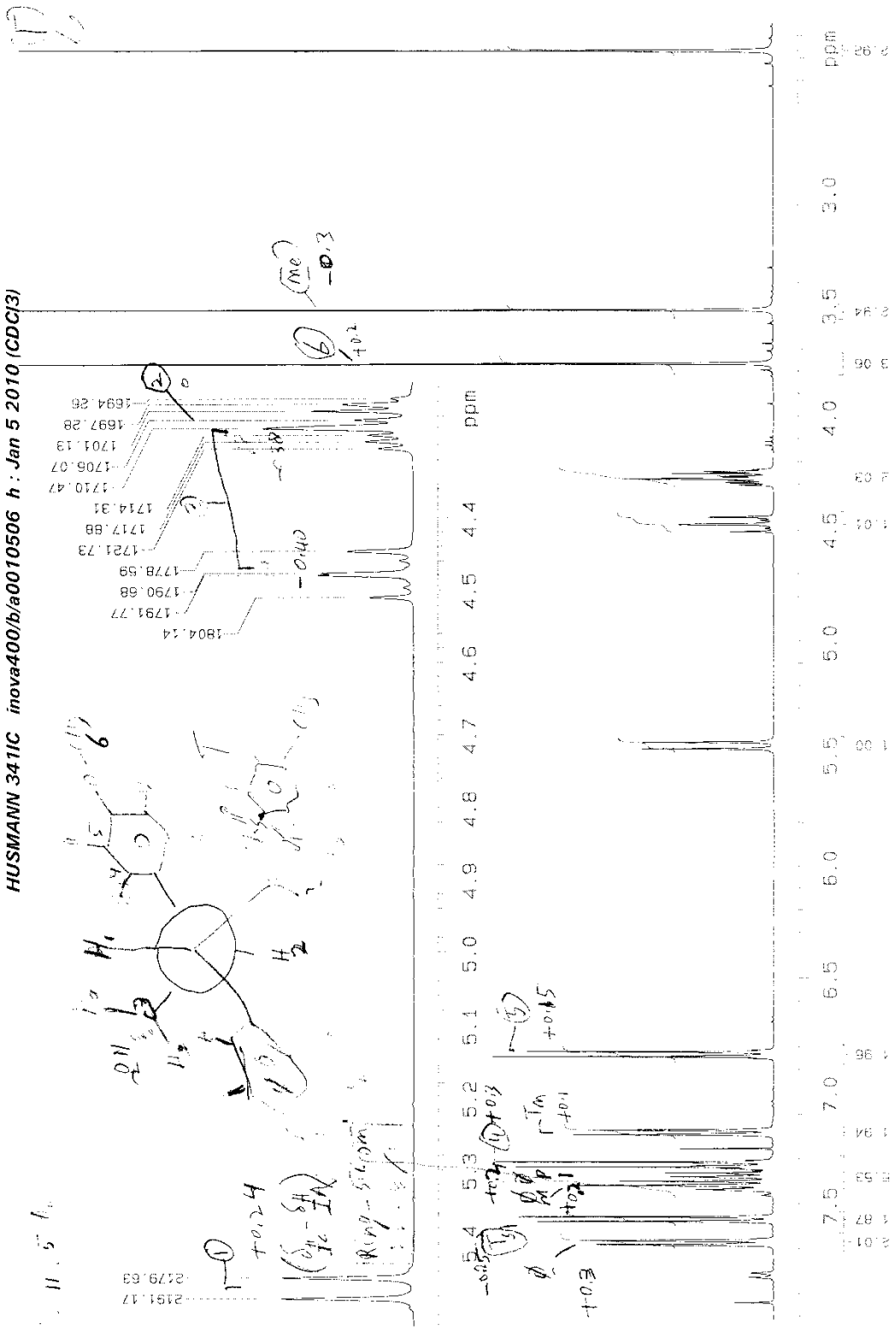



HUSMANN 3411A inova400/b/a0010505 h : Jan 5 2010 (CDCl3)
ppm

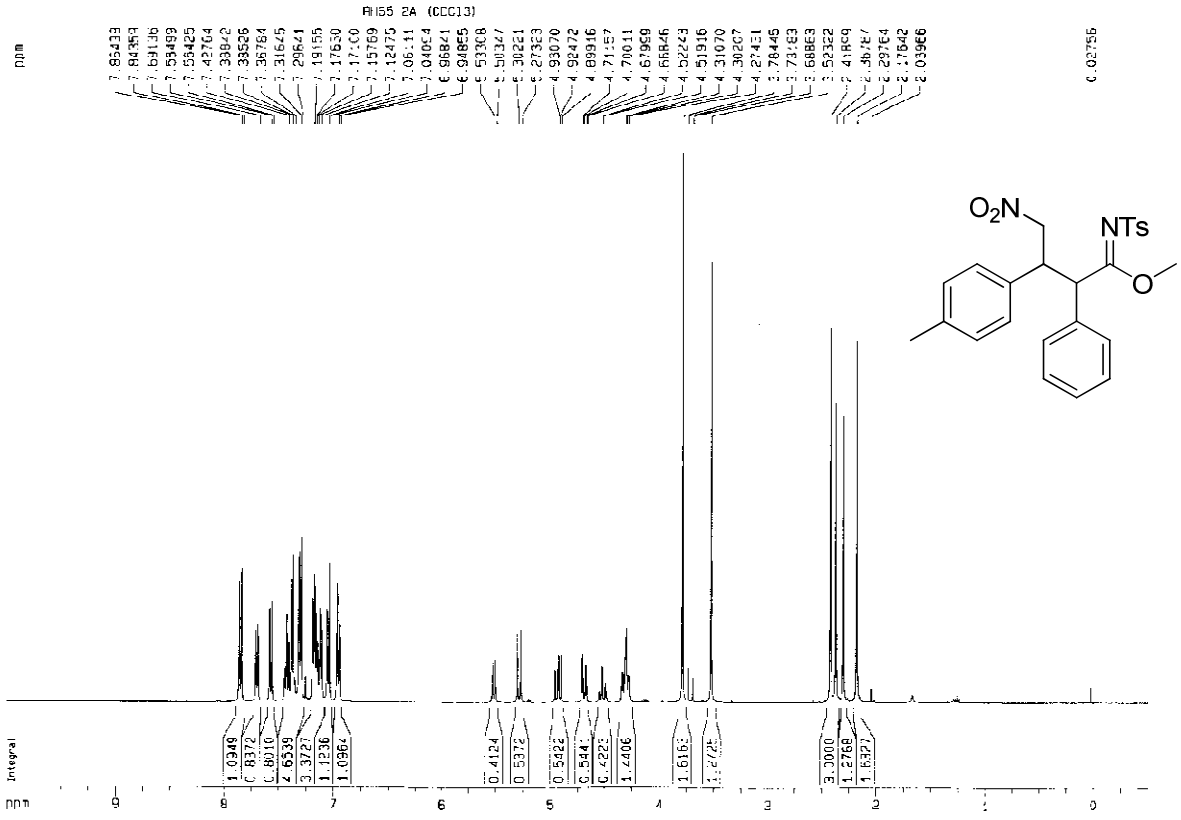
anti Methyl 3-(4-methoxyphenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (Table 2, entry 5)

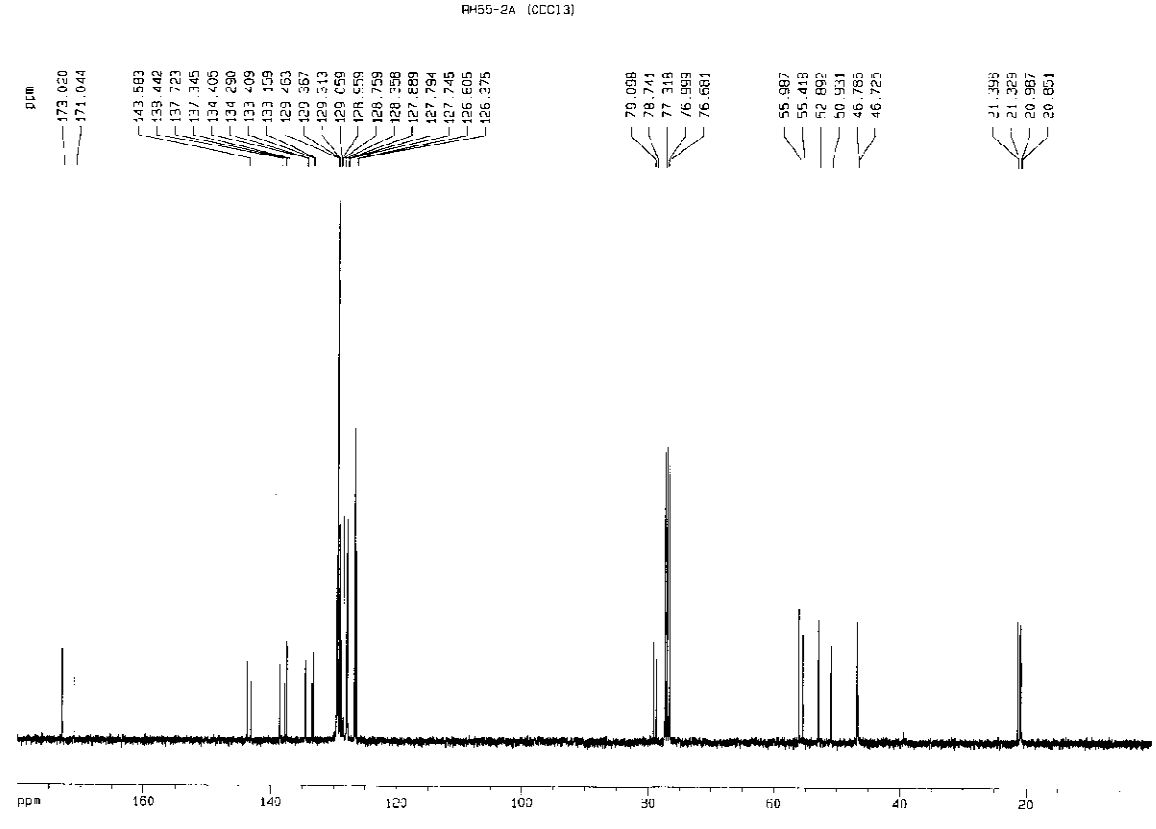




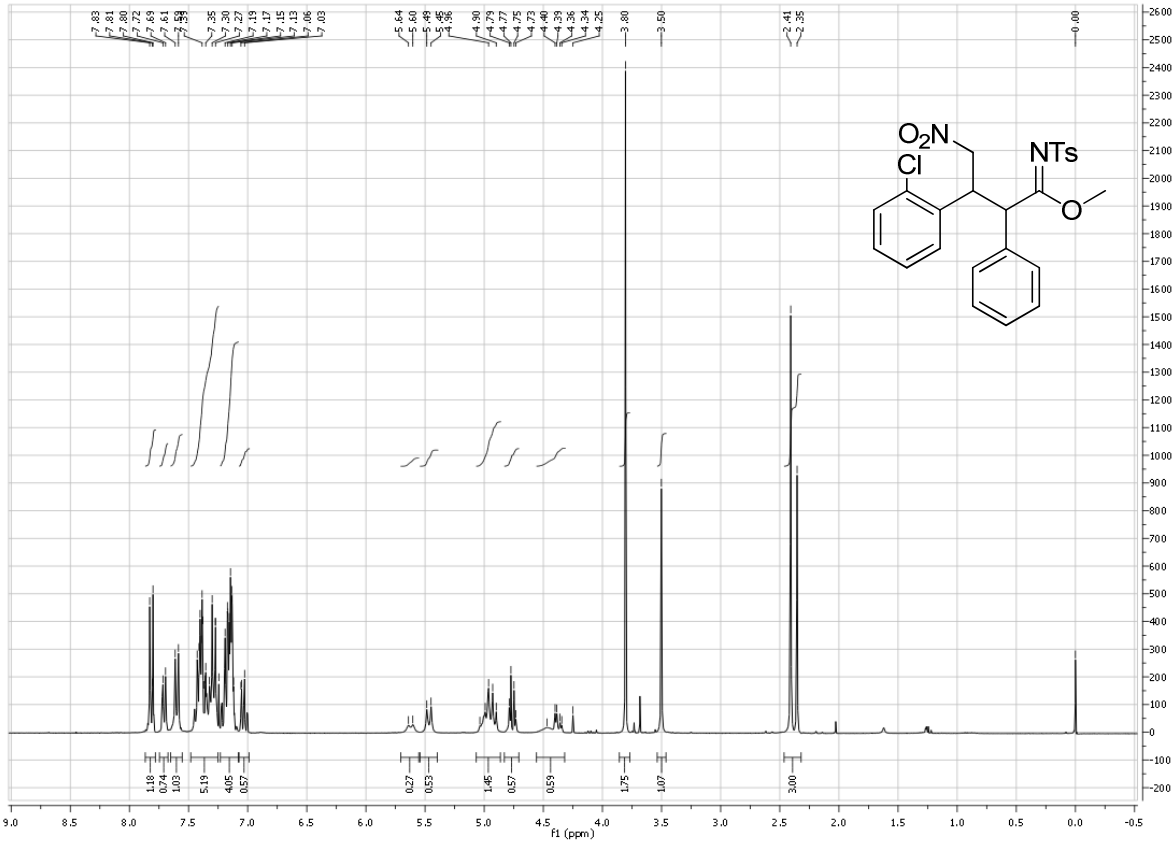

HUSMANN 341IC inova400/b/a0010506 h : Jan 5 2010 (CDCl3)
ppm

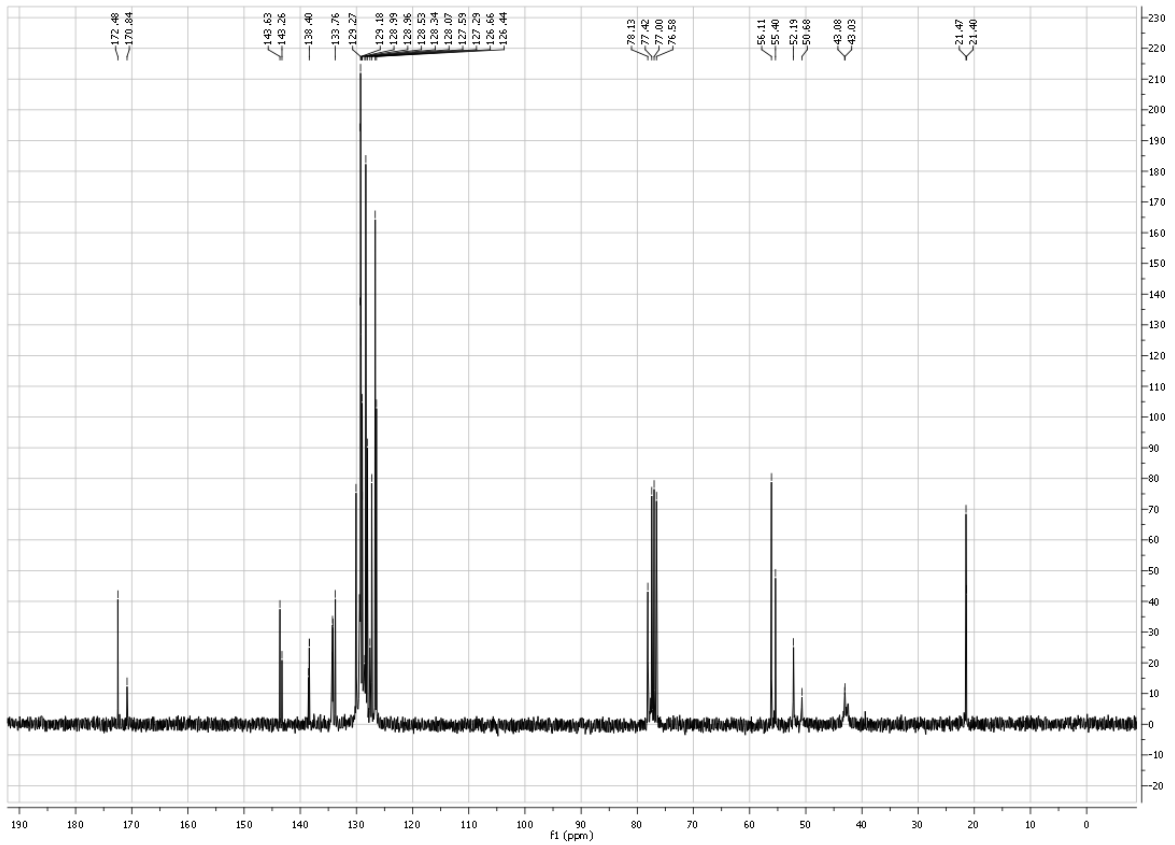
Methyl 4-nitro-2-phenyl-3-*p*-tolyl-*N*-tosylbutanimidate (Table 2, entry 6)



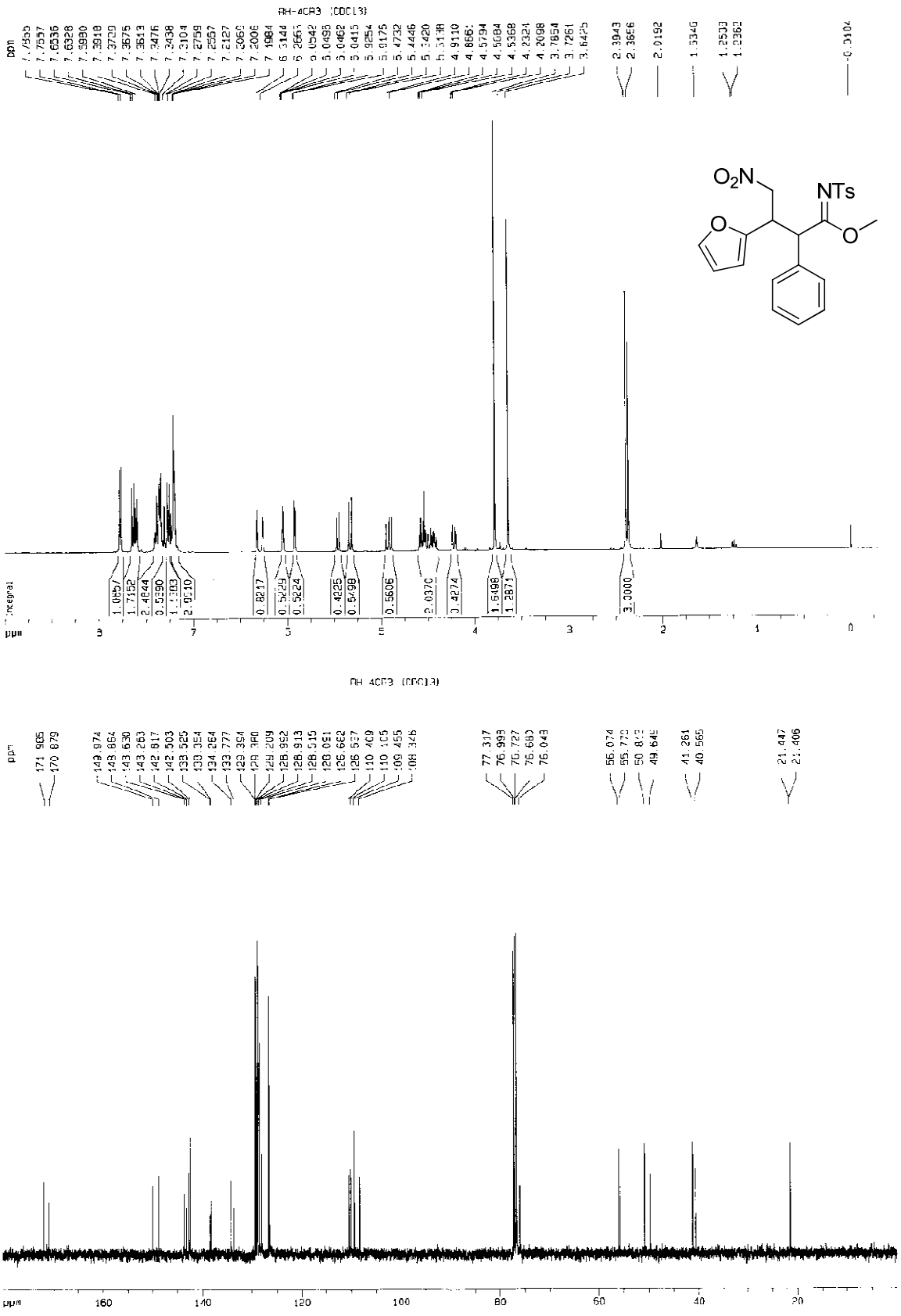


Methyl 3-(2-chlorophenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (Table 2, entry 7)

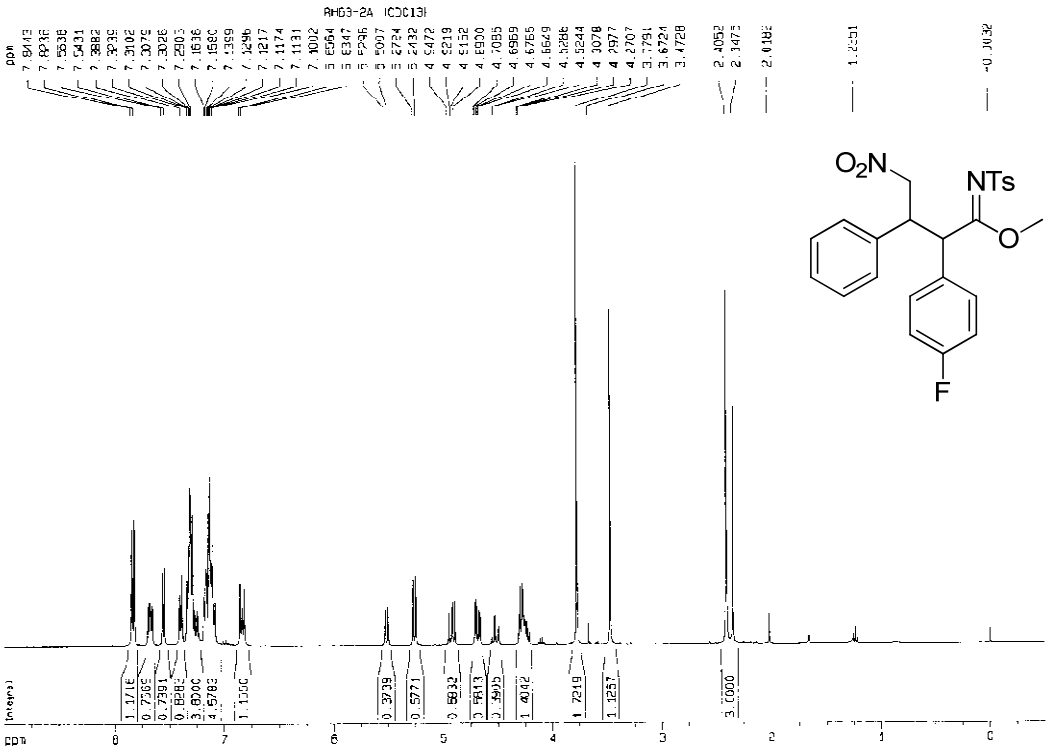


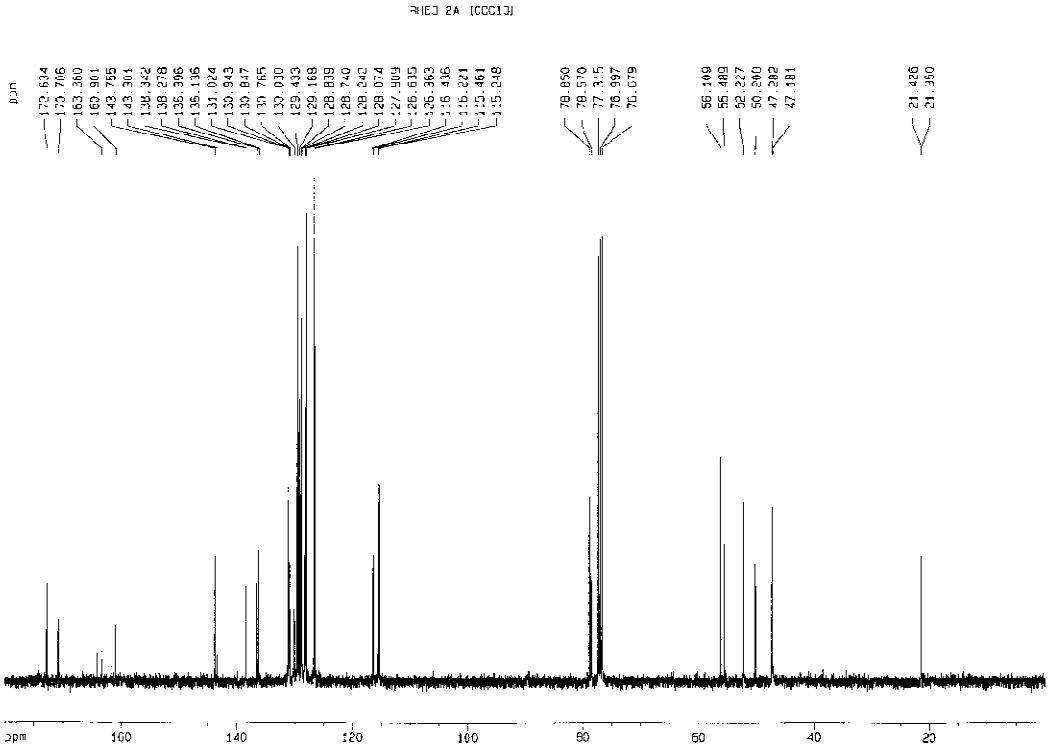


Methyl 3-(furan-2-yl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (Table 2, entry 8)

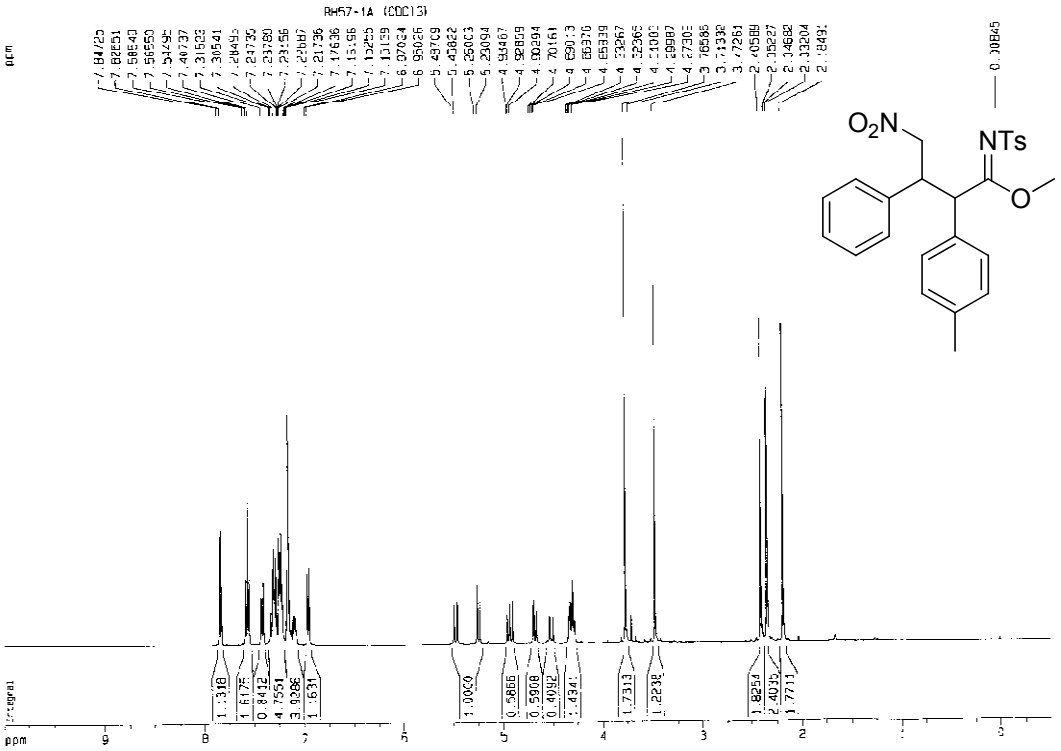


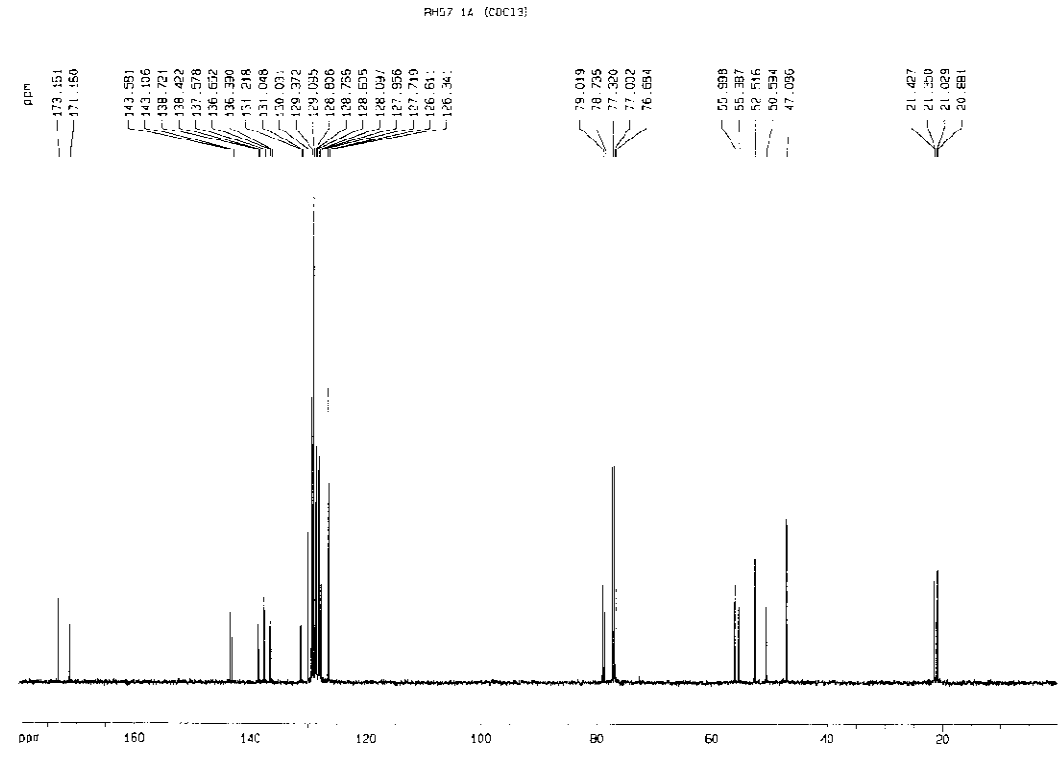
Methyl 2-(4-fluorophenyl)-4-nitro-3-phenyl-*N*-tosylbutanimidate (Table 3, entry 1)



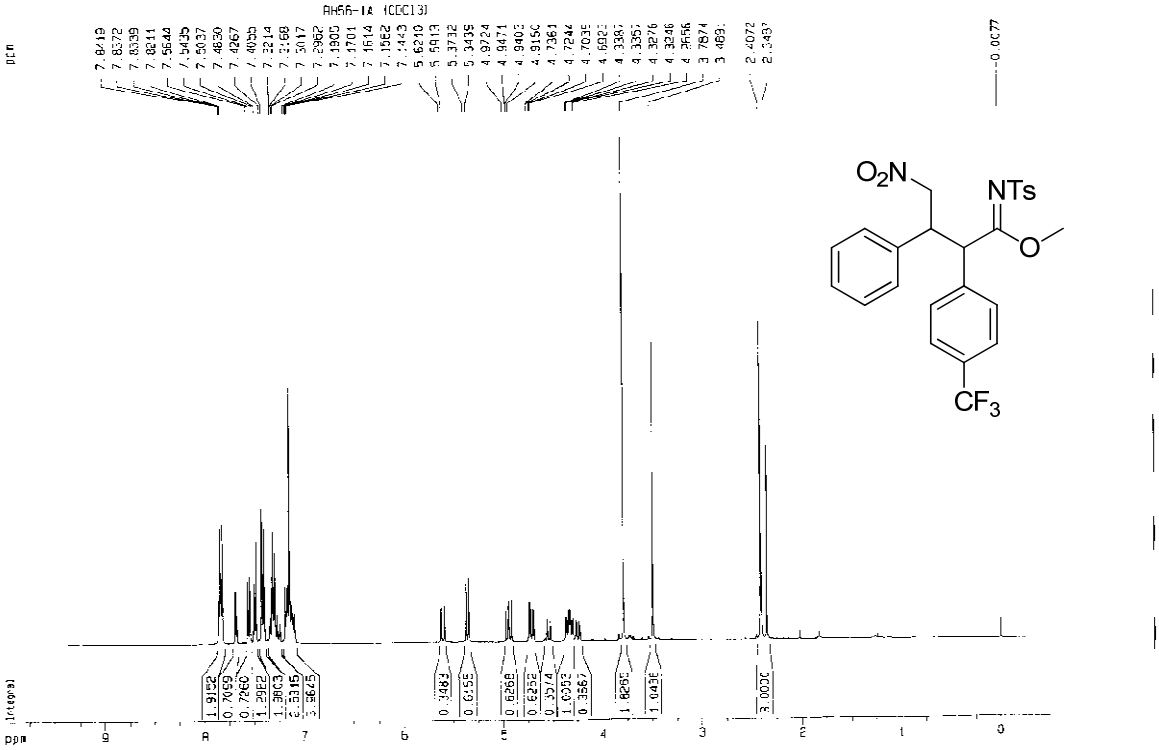


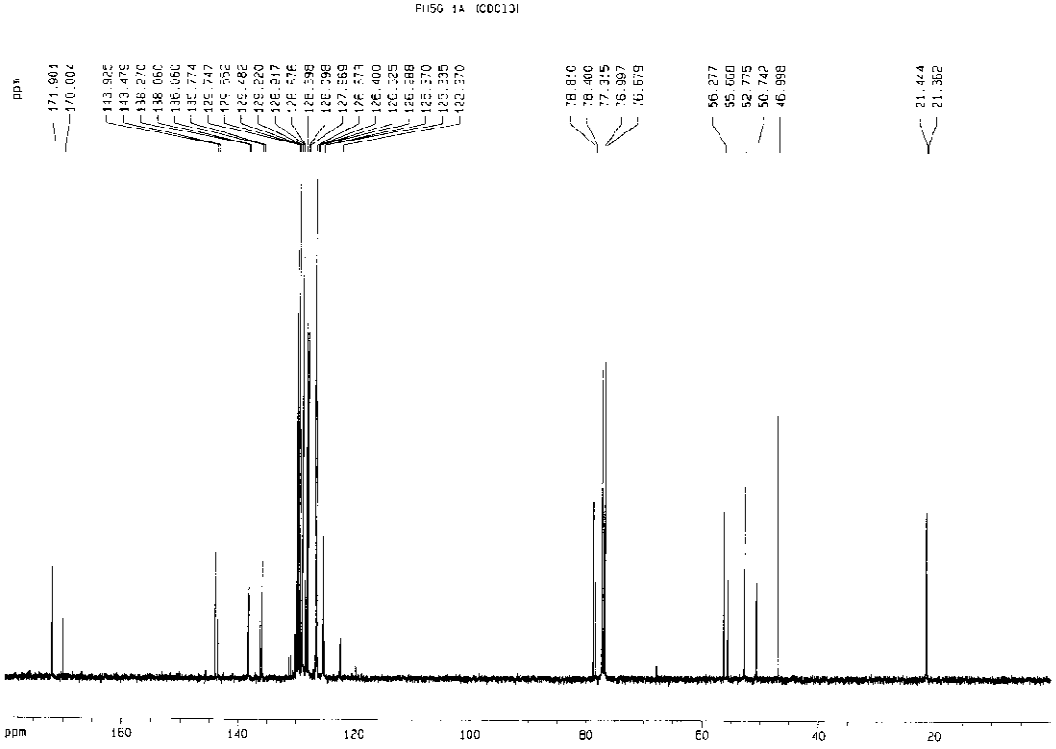
Methyl 4-nitro-3-phenyl-2-*p*-tolyl-*N*-tosylbutanimidate (Table 3, entry 2)



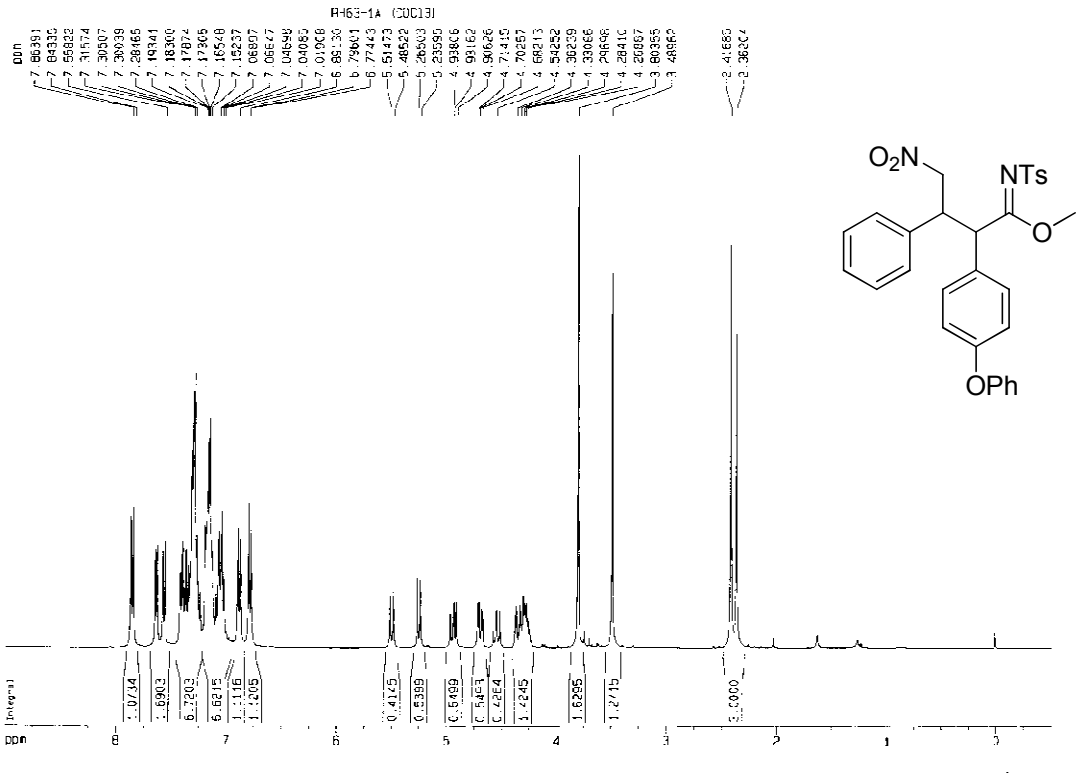


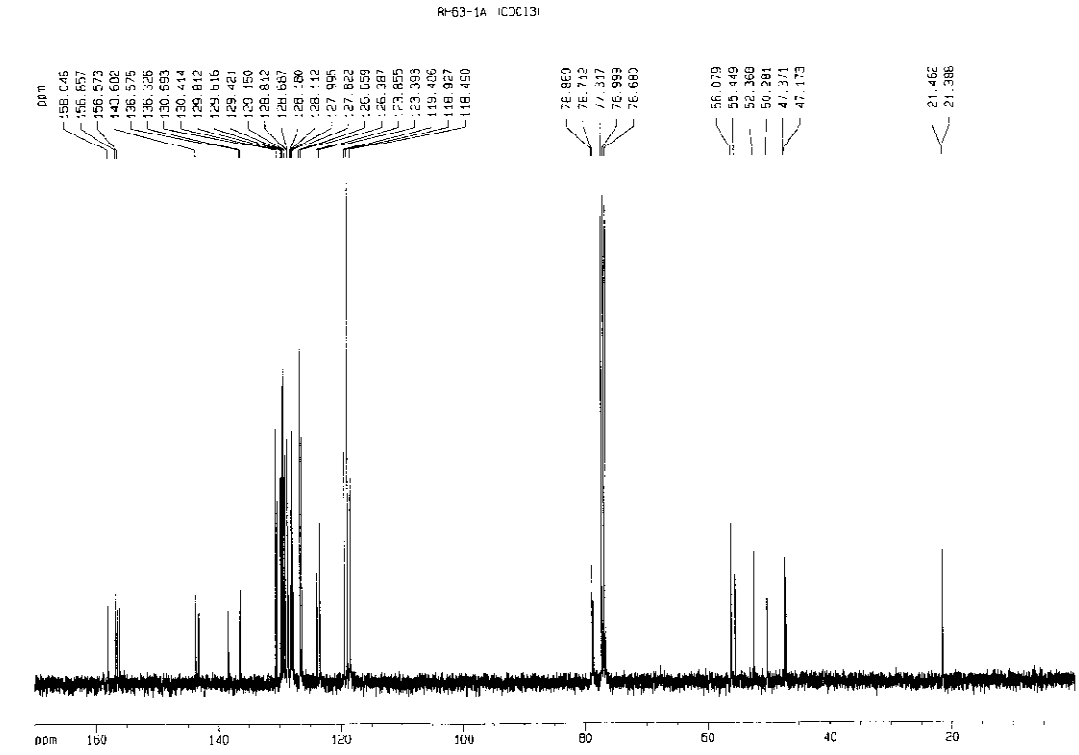
Methyl 4-nitro-3-phenyl-*N*-tosyl-2-(4-(trifluoromethyl)phenyl)butanimidate (Table 3, entry 3)



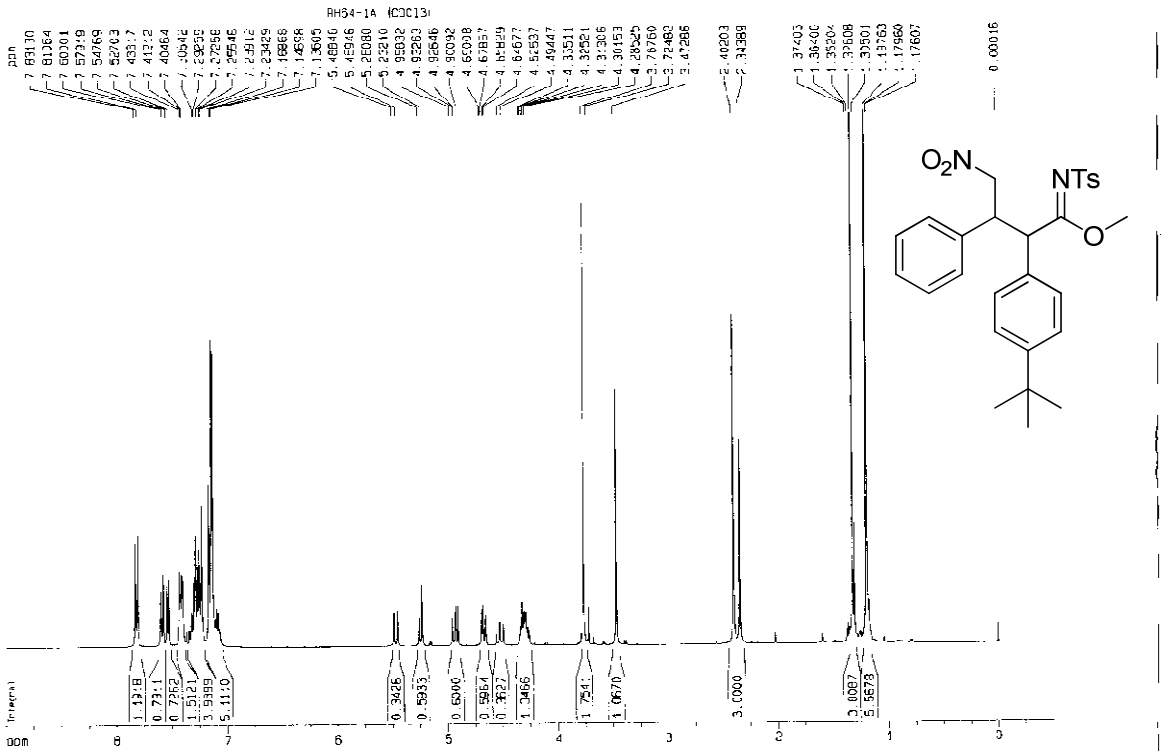


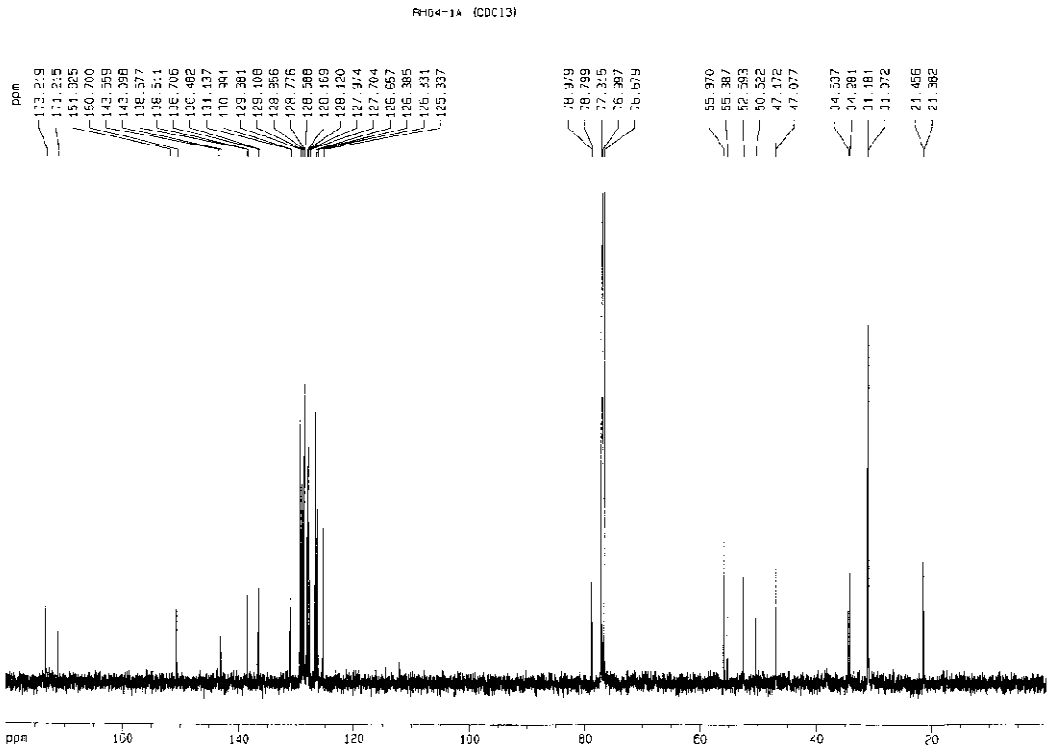
Methyl 4-nitro-2-(4-phenoxyphenyl)-3-phenyl-*N*-tosylbutanimidate (Table 3, entry 4)



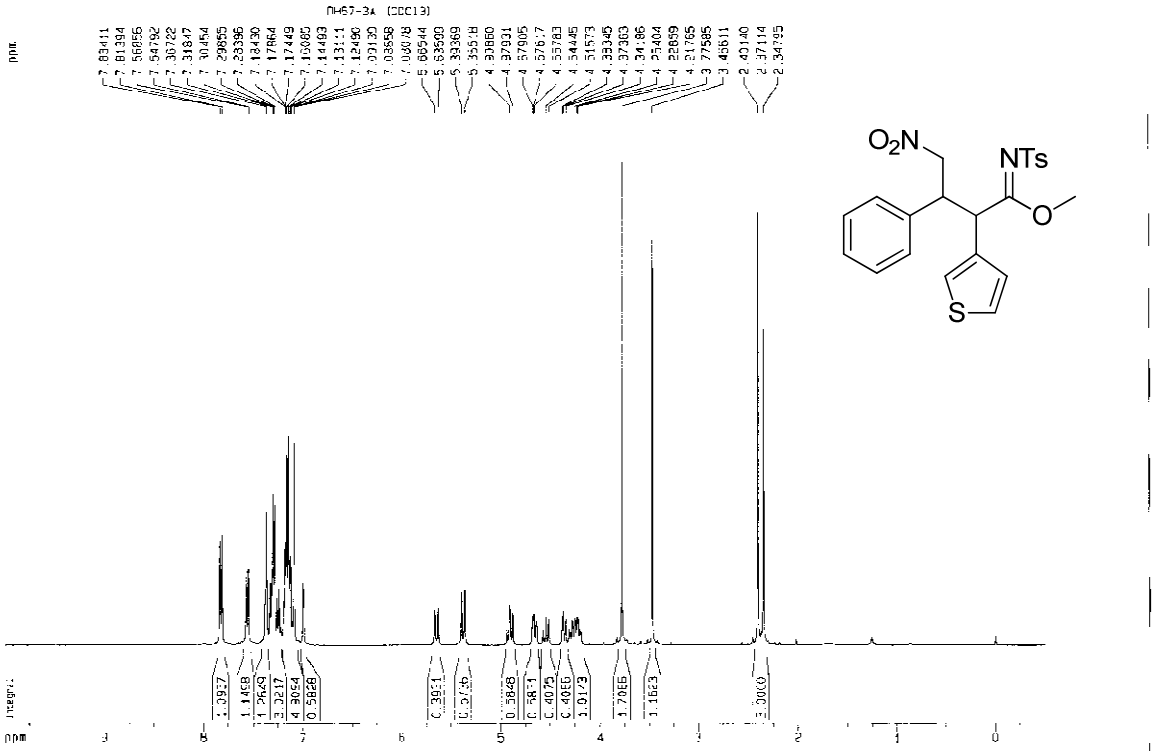


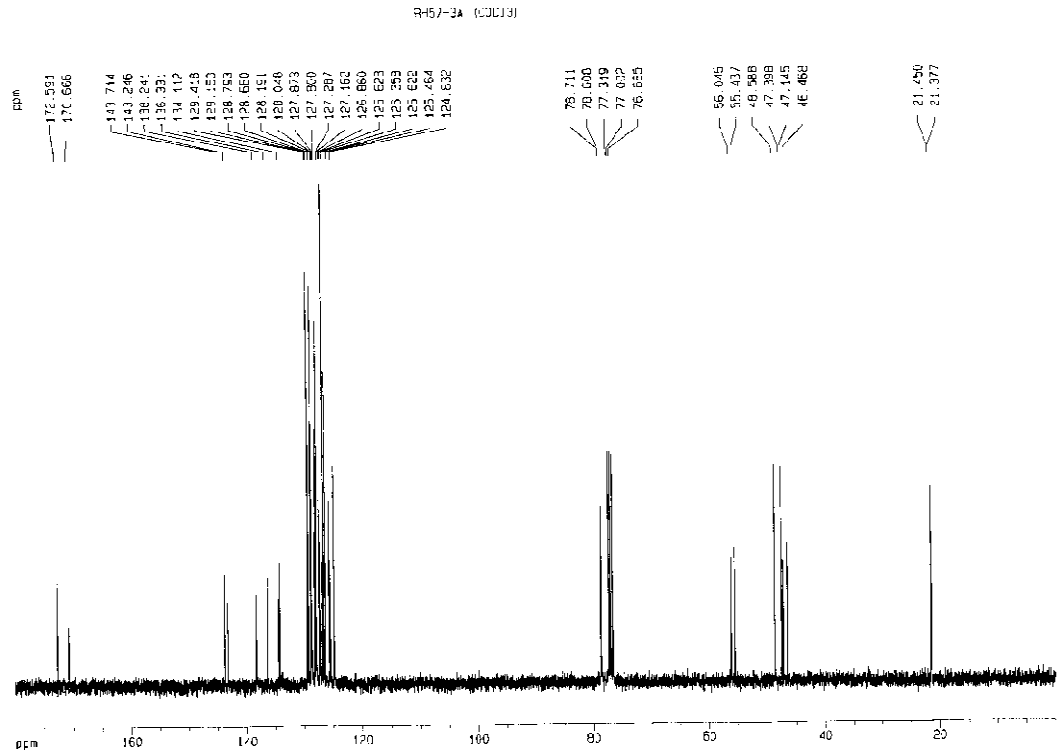
Methyl 2-(4-*tert*-butylphenyl)-4-nitro-3-phenyl-*N*-tosylbutanimidate (Table 3, entry 5)



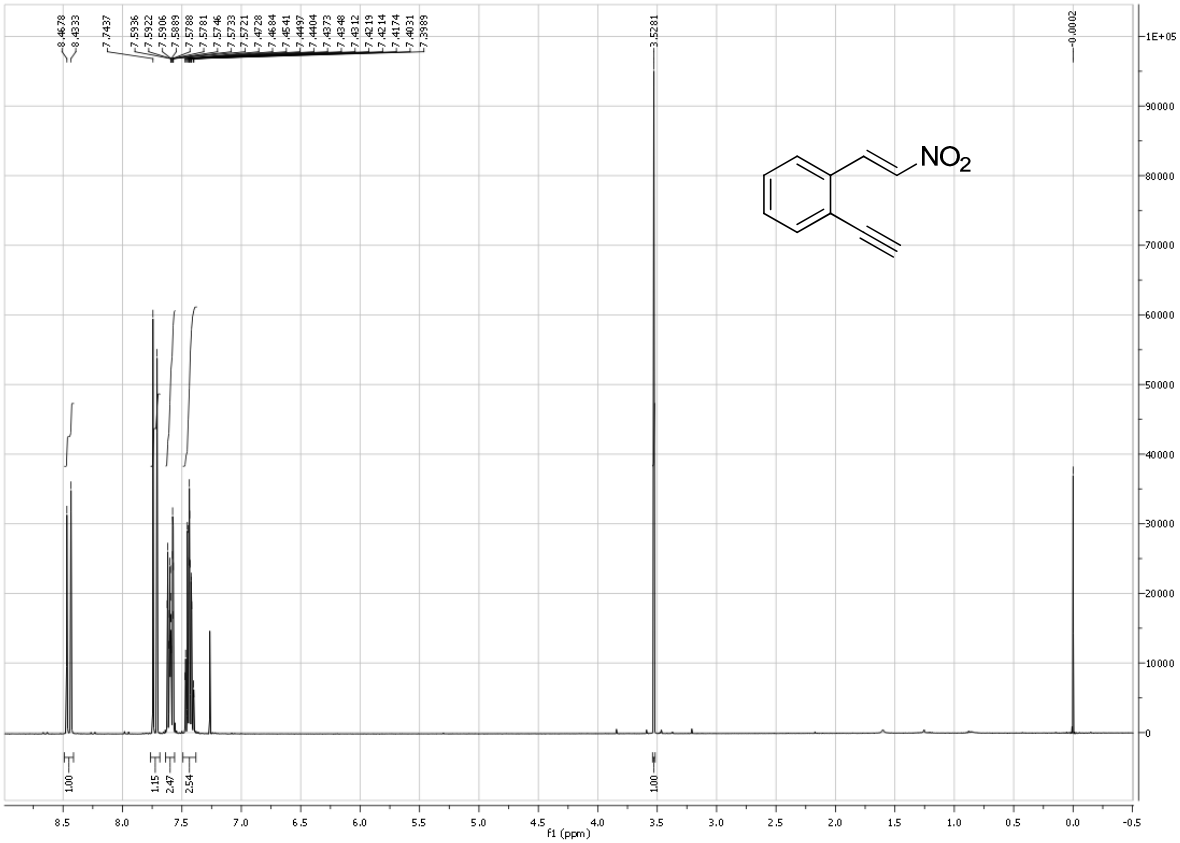


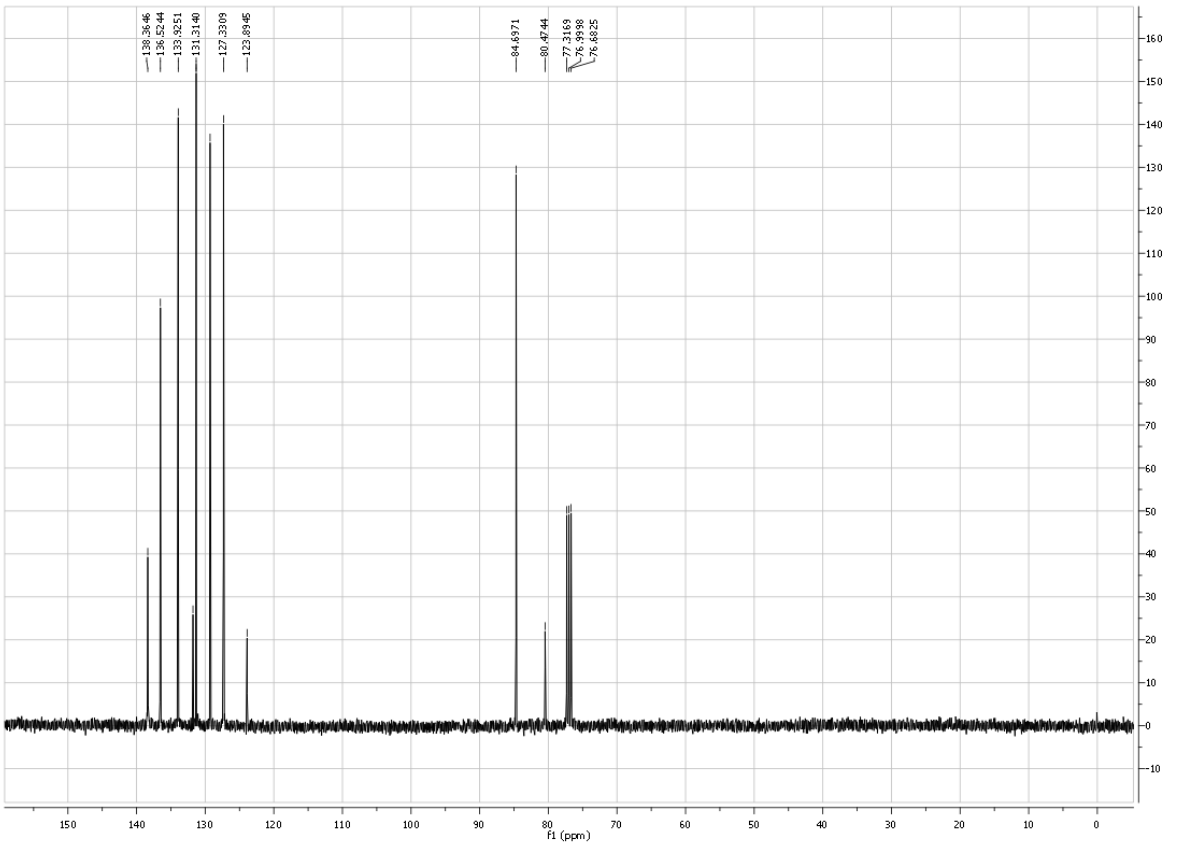
Methyl 4-nitro-3-phenyl-2-(thiophen-3-yl)-*N*-tosylbutanimidate (Table 3, entry 6)





(*E*)-1-ethynyl-2-(2-nitrovinyl)benzene (Scheme 2, compound 5)





3-Methoxy-1-(nitromethyl)-2-tosyl-1,2-dihydroisoquinoline (Scheme 2, compound 6)